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A COMPARISON OF INTRANASAL AND ORAL SCOPOLAMINE FOR MOTION SICKNESS PREVENTION IN MILITARY PERSONNEL

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Executive Summary

Motion sickness in astronauts, aviators, and military personnel often leads to decrements in operational performance. The anti-motion sickness medication, scopolamine, is effective; however, oral and transdermal administrations have proven problematic due to slow absorption, low bioavailability, unpredictable therapeutic effect, potential medication loss due to emesis, and side effects. Although efficacy and side-effect characteristics of intranasally administered scopolamine have not been established, results from preliminary studies indicate intranasal scopolamine has faster absorption, higher bioavailability, and a more reliable therapeutic index than equivalent oral or transdermal forms. The purpose of this study was to compare the efficacy, side-effect profile, and pharmacotherapeutics of a 0.4 mg dose of intranasal scopolamine gel and a 0.8 mg dose of oral scopolamine. It was hypothesized that intranasal delivery of scopolamine would rapidly achieve therapeutic concentrations at lower doses compared to oral scopolamine while minimizing medication-induced performance impairment. To test these hypotheses, 54 aviation candidates, 50 male and 4 female, were recruited and randomized to one of three treatment groups [intranasal scopolamine gel (IN SCOP); oral scopolamine (PO SCOP); or placebo] and then exposed to passive Coriolis cross-coupling for 40 minutes or until moderate nausea was reported. Medication efficacy was determined by number of head movements tolerated among groups and pharmacotherapeutics for IN SCOP and PO SCOP were determined by salivary assay. Side-effect profiles for all groups were derived from performance on a cognitive battery, measurements of near-focus visual accommodation (VA), scores on the Karolinska Sleepiness Scale (KSS) and motion sickness questionnaires. Analysis detected no significant differences in the number of head movements tolerated among groups, $p > 0.05$. Pharmacotherapeutic data show increased scopolamine absorption and decreased time to reach maximum salivary concentration with intranasal administration (T_{max} = 1.463 ± 0.98 hr, C_{max} = 54.857± 103.739 ng/mL, AUC = 51.732 ± 93.802 ng*h/mL). No treatment effects were detected over time on the cognitive battery, VA, or KSS, $p > 0.05$. An ANOVA revealed a significant decrease in heart rate over time for IN SCOP and PO SCOP versus placebo at several time points post-dose, while no clinically significant differences were found for systolic or diastolic blood pressures. A negative linear relationship was found between Motion Sickness Susceptibility Questionnaire (MSSQ) scores and number of head movements (r = - .24, $p < .05$). The present study lacked sufficient power to draw definitive conclusions regarding efficacy or to make adequate comparisons between the two medications, F (2, 50) = 0.743, $p > .05$, observed power = 17 %, however; medication absorption was significantly greater for IN SCOP at one-half the dose (0.4 mg v. 0.8 mg) with no side effects or detrimental impact to performance.

Introduction

Impact of Motion Sickness on the Military and Astronauts

The detrimental impact of motion sickness on military personnel and astronauts has been well established. Many military occupations regularly place personnel at risk for motion sickness during aviation, naval, and combat missions. For example, airsickness has been a recognized impediment in the training and selection of pilots, navigators, and other aircrew since the turn of the century (Chinn, 1951a; Wood, Graybiel, McDonough & Kennedy, 1965). Although few verifiable statistics exist on attrition of naval aircrew due to motion sickness, a review of the literature indicates 10-38% of student pilots and approximately 50% of navigators show some degree of airsickness during training with concomitant decreases in flight performance ratings (Banks, Salisbury & Ceresia, 1992; Dobie, 1974; Money, 1970). In addition, motion sickness is the stated cause of attrition for an estimated one percent of student pilots and 5% of student navigators (Banks et al.; Brand, 1970; Chinn, 1951b; Dobie & May, 1994; Hixson, Guedry & Lentz, 1984; Jones, Levy, Gardner, Marsh, & Patterson, 1985; Money, 1970; Royal, Jessen & Wilkins, 1984; Ryback, Rudd, Matz, & Jennings, 1970; Wood et al., 1965). A review of the seasickness literature reveals that 10-90% of naval personnel are susceptible to episodes of seasickness, depending upon the motion of the ship (i.e. mild vs. severe), and that this seasickness affects crews' motivation and performance on cognitive and motor tasks (Stevens & Parsons, 2002). Seasickness has been positively correlated with motion sickness caused by other modes of transportation; however, the motion stimulus involved with seasickness often elicits more severe symptoms than stimuli from airplanes, trains, and cars (Pethybridge, 1982). Finally, in recent studies examining military land maneuvers in amphibious assault vehicles, 74% of Marines reported moderate to severe symptoms, such as headache, nausea, malaise, anorexia, and emesis, while working at computer workstations (Cowings, Toscano, & DeRoshia, 1998; Cowings, Toscano, DeRoshia & Tauson, 1999; Rickert, 2000). Rickert (2000) and Schipani, Bruno, Lattin, King and Patton (1998) demonstrated that military personnel conducting mission operations in this provocative motion environment exhibited significant performance decrements on cognitive tasks requiring time sharing, selective attention, inductive reasoning, memorization and spatial orientation.

Motion sickness in dynamic operational environments is not limited to the military. Data collected from Space Shuttle missions report 70-80% of astronauts suffer from Space Adaptation Syndrome (or space motion sickness) during the first 2-3 days in microgravity and many suffer from post-flight readaptation sickness upon return to Earth (Davis, Vanderploeg, Santy, Jenning & Stewart, 1988; Heer & Paloski, 2006; Reschke et al., 1998). Work schedules and mission events are typically developed on a flexible timetable and extra vehicular activities are not scheduled during the first three days in space to accommodate the potential impact of motion sickness on crewmembers. Although the symptoms of space motion sickness are similar to motion sickness caused by other modes of transportation, the etiology of space motion sickness remains unknown. In addition, attempts to predict susceptibility in astronauts have been unsuccessful due to the lack of correlation between space and earth-based motion sickness. According to Heer and Paloski, lacking the ability to predict susceptible crewmembers, a fast-acting, rescue medication without significant side effects would be an ideal treatment regimen. This type of rescue-oriented countermeasure would aid in ensuring optimal performance during

relatively short space flights (5-10 days) (Davis et al.), and would also be beneficial for high-tempo military operations.

Scopolamine for Motion Sickness

A variety of pharmaceutical countermeasures have been tested for military and space environment application (i.e., anticholinergics, antihistamines, antimuscarinics, and CNS stimulants), with several decreasing the symptoms of motion sickness, but efficacy varies widely and detrimental performance side-effects are common (Cornum, Caldwell & Cornum, 1997; Cowings et al., 1996; Golding & Stott, 1997; Marcus & Furman, 2006; Putcha, 1999; Wood & Graybiel, 1968). The most widely used medication, and perhaps the most extensively researched, is the anticholinergic drug scopolamine. Scopolamine, in oral and transdermal form, has been used in space but slow absorption and lack of efficacy after symptom onset caused removal of these medications from the astronaut's formulary. The current countermeasure of choice for U.S. astronauts is intramuscular injection of promethazine (Bagian, 1991; Cowings et al., 1996; Davis, Jenning, Beck & Bagian, 1993; Putcha, 1999), despite the fact that effective doses can cause drowsiness, affect vigilance tasks, and often require the addition of a stimulant such as dextroamphetamine (Putcha, 1999). The U.S. Navy is currently using a variety of anti-motion sickness pharmaceuticals to preserve optimal manning and individual performance for personnel in challenging motion environments, such as: ScopDex, an oral combination of scopolamine and dextroamphetamine, the transdermal scopolamine patch, meclizine, and promethazine (Ambrose et al., 1991). These medications have proven effective for some, but most have negative performance impacts and none have shown efficacy after symptom onset (Ambrose et al.; Bagian & Ward, 1994; Chinn, Hyde & Milch, 1955; Estrada, LeDuc, Curry, Phelps & Fuller, 2007; Homick, Kohl, Reschke, Degionanni & Cintron-Trevino, 1983; Putcha, Cintron, Tsui, Vanderploeg & Kramer, 1989).

Many of the limitations found with scopolamine appear to be linked to route of administration. Scopolamine has been tested in various forms, from intraveneous (IV) to transdermal patch, with significant variation in outcome and viability for use in motion environments. IV scopolamine is 100% bioavailable, quickly absorbed, and efficacious, but is not conducive for use in dynamic motion environments (Brand, 1970; Ebert, Siepmann, Oertel, Wesnes & Kirch, 1998; Putcha et al., 1996). Oral scopolamine is easily administered; however, first-pass metabolism decreases bioavailability to a range of 11-48% (Putcha et al., 1989; Renner, Oertel & Kirch, 2005) and increases time to reach therapeutic concentration (75-90 min). Another disadvantage of oral scopolamine is the potential for medication loss due to emesis. Transdermal scopolamine avoids first-pass metabolism, but data from several studies reveal extremely slow absorption and extended time to reach therapeutic concentration (8-12 hrs) (Fung, Ho, Lee, Munaretto & Tsai, 2003; Nachum et al., 2001; Parrott, 1989). Other factors which make transdermal scopolamine less advantageous are the high priming dose delivered at application and the design to deliver a sustained release of approximately 1.0 mg for up to 3 days. During the 72-hour delivery, plasma levels are at the highest end of the therapeutic range and have resulted in an increased side-effect profile for many individuals (Parrott, 1986; Renner et al., 2005). Studies have shown extreme inter-individual differences in the plasma concentration achieved with transdermal scopolamine owing to differences in epidermal thickness, skin temperature during use, and variance in drug dose from patch to patch (Fung et

al., 2003; Parrott, 1989). In addition, several investigators have reported severe side-effects, such as hallucinations, recurring migraines, amnesia-like episodes with successive patch use, and continued symptoms for an average of 15 hours following patch removal (Fung et al., 2003; Gordon, Mankuta, Shupak, Spitzer & Doweck, 1991; Wilkinson, 1987).

Early Intranasal Scopolamine Research

Understanding the limitations of oral and injected medications in an operational environment, early military research involving scopolamine explored intranasal instillation in the form of drops and spray (Chinn, et al., 1955; Chinn, Milch & Dugi, 1953; Hyde, Tonndorf & Chinn, 1953; Tonndorf, Hyde, Chinn & Lett, 1953). The study conducted by Tonndorf, et al., (1953) compared subcutaneous, oral, and intranasal scopolamine and found the absorption of intranasal scopolamine to be comparable to subcutaneous in rate and "completeness." Chinn et al., (1953; 1955) and Hyde et al., (1953), found analogous absorption results for intranasal scopolamine, however, they also reported a decrease in dose required to reach therapeutic levels, leading to a significant reduction in side effects. For example, marked vomiting in these studies was decreased by almost 40% with administration of only 0.2 mg of scopolamine. Chinn et al., (1953; 1955) also tested intranasal scopolamine's anti-motion sickness properties using a swing test in one experiment and standardized in flight turbulence in a second. Intranasal scopolamine (0.3 mg) was given prophylactically in the swing test experiment and results showed that intranasal administration conferred approximately 40% greater emesis protection when compared to placebo. The rapid medication absorption and protection afforded in the swing test suggested exploring the therapeutic properties of intranasally delivered scopolamine. In the second experiment, Chinn et al., (1955) used military aircraft to provide a standardized, provocative stimulus with subjects being treated 15 minutes after take-off, a time based on previous flights where no vomiting would have occurred, however, vasomotor disturbances and nausea would be present. The data clearly showed that intranasal administration given after symptom onset significantly reduced the incidence of vomiting, while oral administration was shown to be "completely ineffective." The delivery methods utilized in these studies were ahead of their time however, the nasal spray technology available during that period posed a challenge for standardization of dosing. The estimated dose delivery was reported to be in error as much as two to three times the intended dose during some of the experiments. In addition to the primitive spray delivery technology, these researchers had no serum methodology to accurately measure bioavailability and, in most studies, absorption results were based solely on changes in salivary flow rates and symptomology.

Recent Intranasal Scopolamine Research

Advances in biochemical formulation and pharmacokinetic analysis over the past 50 years have led to the development of stable, bioadhesive compounds for nasal spray and gel delivery of medications. Recent studies investigating the bioavailability and efficacy of intranasal scopolamine have provided more objective results than earlier studies. Putcha et al., (1996) compared the pharmacokinetics of oral and intranasal scopolamine and showed that intranasal administration of scopolamine drops achieves greater bioavailability (83 v. 3.7%), decreased time to reach therapeutic concentration than an equivalent oral dose (0.37 hr vs. 0.78 hr), and a similar magnitude of effect and duration compared with IV dosing. Klocker,

Hanschke, Toussaint & Verse (2001) in the only published study investigating the efficacy, safety, and tolerability of intranasal scopolamine determined that an intranasal scopolamine spray, at a concentration of 0.2%, significantly reduced symptoms of simulated seasickness when compared to dimenhydrinate and placebo with no anticholinergic side effects or adverse events reported. These initial findings related to intranasal scopolamine indicate potential use as a reliable, fast-acting, operationally compatible, motion sickness countermeasure for prophylaxis, and potentially, rescue treatment.

Objectives and Hypotheses

The objectives of this study were, first, to determine if intranasal scopolamine gel would confer greater motion sickness protection than oral scopolamine and/or placebo while decreasing medication-induced performance impairment, and second, to determine if a 0.4 mg dose of intranasal scopolamine gel would achieve therapeutic concentrations at a faster rate compared to the standard 0.8 mg dose of oral scopolamine. The following hypotheses were examined: (1) intranasal scopolamine will afford greater protection against a provocative motion stimulus, increasing the number of head tilts tolerated, compared to oral scopolamine and placebo, (2) a smaller dose of intranasal scopolamine will achieve faster bioavailability, reach a higher maximum salivary concentration (C_{max}) in less than half the time, and an increased therapeutic level as compared to oral scopolamine, and (3) no difference will be detected in performance on cognitive tests and side effects reported via questionnaires when the IN SCOP group is compared to the PO SCOP and placebo groups. For clarity, the acronyms IN SCOP and PO SCOP will only be used when specifically referring to the intranasal (IN SCOP) and oral scopolamine groups (PO SCOP) tested in this study.

Method

Sample and Apparatus

Subjects. Fifty-four aviation candidates (50 males and 4 females) with an age range of 21-31 years (mean = 23.4 yrs, *SD* = 2.7) voluntarily participated in this study. All volunteers had a current physical and were medically screened by a physician to ensure safety. The protocol was approved by the Naval Aerospace Medical Research Laboratory (NAMRL) Institutional Review Board (IRB). Each subject provided written informed consent before participating in the study. Descriptive statistics for the groups are summarized in Table 1.

Motion stimulus. The Human Disorientation Device (HDD; Appendix 1) provided passive, Coriolis cross-coupling stimulation by rotating the subject about the earth's vertical and horizontal axes in combination (Hixon & Niven, 1969). Subjects sat in a chair, located inside a metal sphere, and were restrained with an aviator-style 4-point seat belt and a padded head fixture to prevent extraneous movement and to ensure head-centered movement during rotation. The subject's gaze was directed to a black visual field inside the device. The staircase profile of counter-clockwise rotation about the vertical began with a velocity of 1 rpm and increased in increments of 1 rpm/min, while rotation about the horizontal consisted of a 40-degree roll to the right, back to center, then left in a 3 second/direction sequence for a maximum of 40 minutes.

Experimental Procedures

The study was a randomized, double-blind, placebo-controlled clinical trial in which subjects served in one of four treatment conditions: IN SCOP gel, PO SCOP capsule, oral dextroamphetamine (D-amphet) capsule, or double dummy placebo (IN SCOP 0.4 mg, PO SCOP 0.8 mg, 10 mg D-amphet or placebo). Results for three of the four groups are discussed in this report. The results of the comparison of D-amphet to placebo have been reported separately in Simmons, Phillips, Lojewski and Lawson (2008).

Subjects were initially screened for inclusion by the administration of a confidential medical questionnaire, and after passing the initial screening, were scheduled for blood work, a physical exam, a cognitive battery, and a visual accommodation test on practice day, followed by a separate motion sickness test day. All subjects retained for the study were instructed to abstain from potentially unsafe or confounding activities 7-days prior to their assigned test day.

Practice day. A practice session for the ARES® cognitive battery and Visual Accommodation (VA) was conducted to ensure performance asymptote was reached prior to actual data collection (Appendix 2). The practice session consisted of six trials of the ARES® administered on a Palm® Pilot PDA (Tungsten E Model; Appendix 3). VA testing consisted of 4 trials using the RAF Rule (Appendix 4). Each subject's test day was scheduled to ensure that no more than 2 days elapsed between the practice session and actual cognitive data collection to offset any performance decay.

Test day. Subjects reported to the lab at 7:15 am, were given a compliance questionnaire, and if applicable, a urine pregnancy test prior to treatment. Once cleared for participation, vital signs and pre-treatment salivary samples were taken and baseline scores on the ARES®, VA and KSS were established. Saliva was collected using the Sarstedt Salivette® collection system (Sarstedt Inc, Nümbrecht, Germany). Vital signs, ARES®, VA, KSS, and salivary samples were taken five times post-dose over three hours. To ensure complete double blinding, each subject received an oral dose and an intranasal dose, one being active and the other a placebo. Subjects randomized to an active treatment condition would receive either PO SCOP (0.8 mg) or IN SCOP (0.4 mg), and the second administration, 45 minutes later, would be a placebo of the opposing route of administration. Subjects in the placebo group received an oral and intranasal (saline-based gel) placebo. All medications were formulated by the Corner Compounding Pharmacy (Houston, TX). Physiochemical properties for the IN SCOP gel (scopolamine hydrobromide trihydrate) were: MW = 438.33 g/mole, pH = 3.5/0.2 mg dose, pKa = 7.55 @ 23º C as established by the formula provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX. Oral dosing occurred at 8:00 am at the conclusion of baseline testing. Forty-five (45) minutes after oral administration subjects received an intranasal dose. The physiological symptoms of motion sickness and the self-report rating system were reviewed prior to the rotation, 75 minutes after oral dosing and 30 minutes after intranasal dosing. For a detailed timeline of test day, see Appendix 5.

Motion Sickness Ratings

The symptom report adapted from the MSQ (Hutchins & Kennedy, 1965) was used to guide the subject's self-report of common motion sickness symptoms including: nausea, dizziness, sweating, increased salivation, warmth, drowsiness, and headache. Subjects were observed remotely by camera, so pallor was not scored. Subjects were asked to rate experienced symptoms as minimal, moderate, or major based on pre-established definitions. Stomach awareness and stomach discomfort were reported as present or not present. One pre-rotation symptom assessment was conducted to determine any pre-existing symptoms and symptoms were also collected at the end of each minute just prior to advancement to the next higher rpm. Finally, one post-rotation assessment was completed to assess recovery prior to the subject exiting the motion device.

Efficacy and pharmacotherapeutics

Efficacy was determined by the average number of head tilts tolerated per group with each minute of stimulation equivalent to 12 head tilts. The stimulus profile was controlled by Labview® software, as was the collection of the total number of head tilts and ride duration. Pharmacotherapeutics of intranasal and oral scopolamine were determined by salivary assay. The subject was instructed to lightly roll a Salivette® in his or her mouth for 2 minutes and then place the salivette® into a tube and seal with the lid. The sealed tube was prepared for shipment and stored in a -80°C freezer. Salivary assays were conducted by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX.

Questionnaires

MSSQ-Short. This questionnaire was designed to determine how susceptible an individual is to motion sickness and what kinds of motion stimuli were most effective in causing sickness during childhood and over the past 10 years. Sickness was defined as feeling queasy or nauseated, or actually vomiting after exposure to a variety of motion stimuli involving land, sea, and air travel, as well as amusement rides (Golding, 2003; 2006). Although not used as a study inclusion criteria, the MSSQ-Short provided a statistically valid means to ensure the groups were equally balanced and representative of the normal population regarding motion susceptibility. The MSSQ-Short has an internal reliability of 0.87 (Golding, 2006).

KSS. The KSS measures sleepiness using a nine point scale based on five states ranging from "extremely alert" to "extremely sleepy, fighting sleep". There are four intermediary states that are not designated with words. Previous research has found that the KSS is closely linked to the objective measures of encephalographic and oculographic signs of sleep onset (Akerstedt & Gilberg, 1990). Scores on the KSS were used to determine the potential impact of medication on alertness.

Cognitive tests

A Palm® Pilot PDA was used to administer the ARES®, a customized, Tri-Service Test Battery of objective cognitive tests consisting of: Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample (Elsmore & Reeves, 2004). Further information regarding ANAM® and ARES® cognitive batteries may be found in Reeves' ANAM® historical perspectives article (2007). These particular cognitive tests were chosen as they are sensitive to medication-induced performance effects (Lewandowski, Dietz, & Reeves, 1997; Elsmore, Reeves & Reeves, 2007; Kane, Roebuck-Spenser, Short, Kabat & Wilken, 2007; Wilken, Sullivan, Lewandowski & Kane, 2007).

Visual acuity assessment

An RAF rule (Neely, 1956) was used to measure visual accommodation (near-focus). Subjects held one end of the rule just under the eyes and looked down the rule at a box, which was mounted on a slide, located at the opposite end. Subjects were instructed to read a line of text printed on the face of the box repeatedly while the box was slowly advanced toward them. Subjects were instructed to say "stop" when the text became blurred. The number (in cm) corresponding to the box location on the rule was recorded as the VA score. The VA test was given to detect potential changes in focal vision with the use of a non-selective, muscarinic antagonist.

Physiological monitoring

The Welch Allyn Propaq Encore® (Model 206 EL) was used to measure blood pressure and heart rate and the Welch Allyn Sure Temp Plus® was used to determine the subject's temperature. This information was collected for safety and to provide additional information regarding potential medication effects. Subjects were queried at regular intervals regarding any adverse events (AE) they may be experiencing and were also instructed to report any AE that deviated from baseline as they occurred. If an AE was reported, the time of onset, duration, pattern (continuous vs. intermittent), relationship of the AE to drug administration, action taken, and outcome were recorded.

Statistical Analyses

Statistical analyses were performed using SPSS version 12.0 for Windows® (SPSS Inc., Chicago, IL). All values are reported as mean ± SE. A Pearson correlation coefficient was calculated to establish the relationship between total head movements tolerated and scores on the MSSQ-Short. A between-subjects analysis of covariance was conducted to test for differences in the number of head movements tolerated (i.e. duration of stimulus) among the three groups (IN SCOP, PO SCOP, and placebo) using MSSQ-Short scores as a covariate. A series of two-factor ANOVAs were conducted on data from the VA, KSS, and the ARES® cognitive battery to examine the side-effect profiles of each treatment condition over time. Specific components of the ARES® cognitive battery used in the side-effect analysis included: Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample. All pharmacotherapeutic data were provided by the Pharmacotherapeutics Laboratory, Johnson Space Center (Houston, TX).

First, mean drug concentrations of IN SCOP and PO SCOP, as a function of time, were plotted for each group. Rates of absorption were then analyzed to determine pharmacotherapeutic variables such as, maximal salivary concentration (C_{max}), time to reach C_{max} (i.e., T_{max}) and area under the salivary-concentration-vs.-time curve (AUC) using non-compartmental analysis in WinNonlin® (Pharsight Inc., Apex, NC). Finally, three, two factor ANOVA's were conducted to compare changes in heart rate, systolic, and diastolic blood pressures among treatment conditions over six time points. In all tests, $p < 0.05$ was considered statistically significant.

Results

The Pearson correlation comparing scores on the MSSQ-Short and the total number of head movements tolerated between groups was significant ($r = -.24$, $p < 0.05$), therefore, a one-way ANCOVA was calculated using scores from the MSSQ-Short as a covariate. The ANCOVA revealed no significant differences for mean number of head movements tolerated among groups F (2, 50) = .743, $p > 0.05$ (Table 2). The mean number of head movements tolerated by treatment group is depicted in (Fig. 1). Results of repeated measures ANOVAs found no significant performance differences for treatment groups over time for either VA or the KSS ($p > 0.05$) (Table 3 and Figures 2 & 3). Likewise, no significant treatment effects were detected over time regarding performance on the four ARES cognitive tasks ($p>0.05$) (Table 4 and Figures 4-7).

[1]Analysis of pharmacotherapeutic data show increased scopolamine absorption (salivary concentration) (C_{maxIN} = 54.857 ± 103.739 ng/mL; C_{maxPO} = 0.361 ± 0.348 ng/mL) and decreased time to reach maximum salivary concentration (T_{maxIN} = 0.1463 ± 0.98 hr; T_{maxPO} =2.792 ± 0.803 hr) with intranasal versus oral administration (Tables 5 & 6). The mean area under the concentration curve (AUC), calculated through the last saliva sample, for intranasal was 51.72 (± 93.6) ng*hr/mL. The AUC, calculated to the last sample, for oral administration was 0.459 (± 0.409) ng*hr/mL. A salivary estimate for bioequivalence revealed that the 0.8 mg oral dose of scopolamine was only 44% as bioequivalent as the 0.4 mg intranasal dose (based on AUClast po/D po) / (AUClast in/D in, where last po = last oral sample; Dpo = oral dose and last in = last intranasal sample; D in = intranasal dose).

Results of an ANOVA examining heart rate and blood pressure readings revealed a significant decrease in heart rate over time for intranasal and oral scopolamine versus placebo at several time points post-dose, F (6.5, 165.73) = 3.62, $p < 0.05$. While no significant drug by time interaction was found for diastolic blood pressure values among the three groups, analysis of systolic blood pressure readings revealed significant group differences between IN SCOP and placebo at baseline and 115 minutes post-IN dose, and between IN SCOP and PO SCOP at 115/160 minutes post-dose and PO SCOP and placebo at 65 minutes post-PO dose. Figure 8 represents mean heart rate data and Figure 9 represents mean systolic and diastolic blood pressure by group.

[1] All pharmacotherapeutic results were provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX.

Discussion

While the present study did not detect significant group differences regarding the number of head movements tolerated among the three treatment conditions, the high degree of variance within groups, the subject variability in motion sickness susceptibility, and the small effect size and insufficient power made it difficult to determine the efficacy of IN SCOP over PO SCOP and placebo. To determine if motion sickness susceptibility was a significant source of variability, the scores on the MSSQ were analyzed and a negative correlation was found between scores and head movements tolerated. The MSSQ scores were then used as a covariate, allowing a small amount of variance due to individual susceptibility to be controlled, resulting in a more accurate indication of medication treatment effect (Fig. 1 and Table 2). Even after controlling for motion sickness susceptibility, there was no significant improvement in power or effect size, and therefore, the lack of significance found with the ANCOVA analysis should not be interpreted as a lack of motion sickness protection afforded by either scopolamine group when compared to placebo (255 ± 27.17 IN; 238 ± 26.90 PO; 210 ± 28.13 Placebo) .

According to the scopolamine concentration data derived from salivary assays provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, intranasal delivery showed increased scopolamine absorption and decreased time to reach maximum salivary concentration compared to oral dosing (Table 5). Concentrations of scopolamine after intranasal administration were assayable at the first saliva sample which was collected 15 minutes post-dose. However, a sample collection time closer to dose time may have revealed a shorter time to maximal salivary concentration. Oral scopolamine concentrations were detected in only 59% of subjects 65 minutes post-dose with very low concentrations reported. These data are in agreement with previous studies indicating that intranasal scopolamine is absorbed at a significantly faster rate than oral, and the onset of action is typically within 30 minutes or less, with therapeutic concentrations of intranasal scopolamine reaching levels significantly higher than oral (Putcha et al., 1996; Ahmed et al., 2000; Klocker et al., 2001).

Although general interpretation of the medication absorption data comparing intranasal versus oral scopolamine was clear, more detailed analyses of pharmacotherapeutic data from both treatment groups were difficult for several reasons. First, salivary concentrations of oral scopolamine were undetectable or extremely low in some subjects and did not show the anticipated decline over time as anticipated, but rather levels increased. Second, the scopolamine concentration values for four intranasal subjects were high and the values for two subjects were extremely high and had to be omitted from the statistical analyses. Third, there were several subjects with erratic scopolamine concentrations, fluctuating from very high levels to zero and then back to normal therapeutic levels. It is hypothesized that these results could be due to the use of salivary assays rather than plasma for reporting scopolamine levels. According to researchers in the field of biochemistry and pharmacology, the primary requisite for use of salivary assays for evaluating the bioavailability of medication is a constant or predictable relationship between the drug concentration in saliva and the drug concentration in plasma (Fatah & Cohen, 2003; Haeckel, 1993; Jusko & Milsap, 1993; Langman, 2007; Margel & Schulz, 2007). Jusko and Milsap (1993) state that the utility of salivary assays for pharmacokinetic and pharmacodynamic studies relies on a drug that exhibits a constant saliva/plasma ratio that is independent of drug concentration, is resistant to changes in salivary

flow, and is consistent among individuals. There are currently no published research studies which establish a predictable relationship between salivary assays of scopolamine and plasma levels. Because this relationship for scopolamine has not been clearly established in controlled experiments, the pharmacotherapeutic data from this study can not be taken as a valid measure.

Further investigation into the use of oral fluid for therapeutic evaluation revealed other considerations and potential problems with the use of this technique. The wide variability in scopolamine concentrations reported in this study, between and within subjects and treatments can be attributed to several factors such as, the type of collection device, salivary flow rate, cross-contamination, the pH of oral fluid, the pKa of the medication, and the fraction of protein binding in saliva and plasma. According to the lab processing the assays, the amount of saliva collected for some subjects was too small to conduct adequate analyses. A decrease in salivary flow for a small percentage of subjects was expected due to scopolamine's anticholinergic effects; however, having samples too small for analysis was not anticipated. The cause may not have been a significant decrease in subject salivary flow, but the salivary collection device, which may not have allowed adequate collection or recovery of the full sample. Fatah & Cohen (2003) investigated the feasibility of using salivary sampling as an alternative to blood and urine and reported that some saliva collection devices result in small sample sizes making accurate analysis difficult. Magerl & Schulz (2007) reported specifically on the Sarstedt Salivette® collection system and stated that this device frequently yields insufficient amounts of saliva to conduct adequate analyses. The preponderance of literature indicates that some collection devices achieve better recovery than other systems, depending on the medication being assayed. Navazesh (1993) compared four differing methods for collecting saliva (draining, spitting, suction, and swab) and emphatically stated that the swab (cotton roll) method was the least reliable. Moreover, different medications require differing amounts of saliva to complete the analysis and no published studies could be found to accurately determine the volume of saliva necessary, or the type of collection device appropriate, for conducting a scopolamine assay (Magerl & Schulz 2007). Salivary flow rate must be taken into consideration, as it is an important factor affecting diffusion of medications, including scopolamine, into oral fluid. According to Jusko & Milsap (1993), changes in salivary flow and time of sampling may complicate the use of saliva for pharmacokinetic purposes. It is possible that even the small dose of scopolamine (0.4mg) used in the present study decreased salivary flow by inhibiting parasympathetic stimulation of secretary glands; this, combined with the inadequacies that may have been inherent within the collection device, may have caused the reporting of abnormal scopolamine levels.

A different concern for oral fluid analysis is intranasal administration of the medication and the possibility of cross contamination from medication passing down the nasal pharynx region into the oral cavity. Klocker et al., (2001) reported six adverse events during an intranasal scopolamine spray study, with most subjects complaining of epipharyngeal scratching and swelling. After examining the extremely high intranasal scopolamine concentrations (175-375 ng/mL) for some subjects in this study, it appears that cross contamination must be considered a plausible explanation. There are no published studies that report the absorptive properties of intranasal scopolamine while using salivary sampling, but Magerl and Schulz (2007) report cases of salivette contamination and associated high drug concentration in saliva with orally administered medications. The results of this study would suggest that salivary sampling may

not be the most effective assessment of drug concentration for use with intranasal drug delivery due to cross contamination yielding unreliable and invalid drug levels.

Haeckel (1993) and Jusko and Milsap (1993) have also determined that the utility of salivary analysis for determining systemic medication levels requires constant pH values of saliva, and is dependent on the pKa of the medication, and the fraction of the drug that is bound in saliva. The variability in pH of the oral fluid influences the saliva to plasma distribution ratio which will greatly impact the ability to accurately detect medication levels (Magerl & Schulz, 2007). Two factors affecting oral fluid pH are changes in salivary flow rate and increased anxiety (Haeckel, 1993). The drug, and nature of this study, would lead one to surmise that both of these parameters were potentially affected. A recent study conducted at this lab calculated salivary pH values ranging from 3.5 – 7.8 for subjects in a motion sickness trial.

Finally, a factor which could significantly impact salivary detection of scopolamine is the chemistry of the intranasal formulation. Bioavailability studies have shown that when dealing with acidic medications, quite often equilibrium favors blood and not saliva and that some medications have rate limiting steps during absorption which limits movement to the oral fluid (Langman, 2007). The intranasal scopolamine formulation used in this study was acidic (pH=3.5 and pKa=7.55 @ 23° C) potentially making saliva absorption values less accurate and reliable. In addition, the degree of drug protein binding will determine the amount of medication available to diffuse to oral fluid (Jusko & Milsap, 1993). The literature shows that the pharmacokinetics of medications in saliva are more complex than those of blood. Future studies should use blood plasma samples to ensure more accurate pharmacokinetic analyses of scopolamine, at least until more controlled studies are published providing answers regarding appropriate methodology for other techniques.

The current study did not find significant cognitive or medication side effects in the IN SCOP group and no adverse events were reported by any subject (Figs. 4-7 and Table 4). The increased rate of absorption and maximal scopolamine concentration was anticipated, but the absence of side effects is in contrast to other studies that reported an increase in the incidence and/or severity of medication-induced side effects with intranasal delivery (Chinn & Smith 1953; Hyde et al., 1953; Ahmed et al., 2000). Chinn et al., (1955) and Putcha et al., (1996) reported an increase in the incidence of dizziness and dry mouth after intranasal administration of doses ranging between 0.2 to 0.6 mg. There have been several studies reporting cases of mydriasis (pupil dilation) after scopolamine administration at higher dosages, such as those delivered by the transdermal patch, however, the present study had no subject reports of changes in visual acuity or reports indicating vision problems after this 0.4 mg intranasal dose of scopolamine. The anticholinergic effects on vision reported in earlier studies may be due to four separate but related facts pertaining to a lack of control of drug dosage. First, Chinn & colleagues and Hyde & colleagues described a distinct variation in the scopolamine quantities administered due to the lack of technological ability to control the spray's emission volumes. Chinn & colleagues returned to scopolamine administration in nasal drop form to achieve more precise dosing. Second, early experiments with intranasal compounds suggested that the scopolamine formulations did not have the correct chemical properties to be readily absorbed through the nasal mucous, requiring a detergent or bioadhesive additive. Following addition of the detergent, the spray was almost too well absorbed, with values several times the amount intended to be

administered. Some of the increase in symptomotology was due to this overcompensation. Third, it was discovered that the acidity of the formulation was important and adjustments in the compound continued until the proper acidity and concentration were determined. A final complicating factor was the inability to accurately measure how much of the scopolamine actually entered the system; rather, pharmacological responses were used as a measure for absorption (Tonndorf et al., 1953). In contrast to earlier studies, the current study was able to utilize a precise drug delivery system to achieve tight control on the amount of scopolamine administered, could physiologically assess the absorption of the medication, and compounded a formula with appropriate characteristics for rapid absorption. The data clearly show a level of systemically available scopolamine that was below the threshold for negative visual or cognitive anticholinergic effects but was clearly absorbed as evidenced by physiological and pharmacologic data.

The analysis of medication effects on physiological variables showed a significant linear decrease in heart rate over time (Fig. 8) with intranasal and oral scopolamine, similar to findings reported by Golding and Stott (1997) using oral scopolamine, Klocker et al., (2001) using intranasal scopolamine and Parrott (1989) administering transdermal scopolamine. The heart rate data from this study indicate that 0.4 mg of intranasal scopolamine and 0.8 mg of oral scopolamine significantly decreased heart rate more than placebo over time, with differences being found at 75, 90, 115, and 165 minutes post intranasal dose and 165 minutes post oral scopolamine dose. The decrease in heart rate was anticipated as administration of a small dose of a muscarinic receptor antagonist acts to block M_1 receptors on postganglionic parasympathetic neurons. The resultant blockade causes an increase in cardiac parasympathetic activity by decreasing the effect of acetylcholine, this is not only seen with scopolamine but also with atropine (Brown & Taylor, 2001). Blood pressure data did not show a significant change over time for diastolic readings among the three groups, however, some differences were seen in systolic values between the IN SCOP and placebo groups at baseline and 115/160 minutes post-dose and IN SCOP v. PO SCOP at 115/160 post-dose, and PO SCOP differed significantly from placebo at the 65 minutes post-dose collection point. Due to the groups being significantly different at baseline, and the lack of clinical significance in the small changes to systolic readings, no clear interpretation can, or should, be given to these particular data. Specifically, no significant change in blood pressures was expected as the systemic vasculature lacks sufficient cholinergic innervation and the vessels supplying skeletal muscles do not appear to be involved in normal regulation of tone (Brown & Taylor). In addition, numerous researchers (e.g. Brown and Taylor; Kanto, Kentala, Kaila & Philajandaki, 1989; and Nachum et al., 2001) reported no significant changes in blood pressure after administration of doses of scopolamine ranging from 0.3 to 0.6 mg through oral, transdermal or parenteral means. However, a study conducted by Klocker et al. (2001) found a significant decrease in diastolic blood pressure after administration of a 0.2% concentration of intranasal scopolamine when compared to dimenhydrinate. The current study found blood pressures, systolic and diastolic, to be very stable but further research comparing blood pressure and bioavailability levels may assist in determining the potential effect of intranasal scopolamine on blood pressure, as well as other physiological variables. The significant decrease in heart rate found in this study is a critical component in confirming the absorption of a small dose of scopolamine, especially in light of the variability in the salivary assay data.

Considerations for Future Studies

Baseline data regarding individual motion tolerance is critical for an adequate comparison of motion sickness prevention treatments. The independent design utilized in this study did not allow for such a comparison. Future studies could benefit from using a within-group design to control individual variability, potentially increasing the study power. In addition, the drug treatment effect may be smaller than anticipated when using a controlled, provocative stimulus, such as the highly nauseogenic stimulus used in this study, again making the repeated measures design better suited for detecting treatment effects if they exist.

Most motion sickness researchers agree that a small percentage of the population is extremely resistant to motion sickness and would not generally benefit from medication. These individuals should be screened out of motion sickness medication studies to ensure conclusions regarding the efficacy of a treatment are valid, and concurrently, to enhance the statistical power by controlling non-treatment related variance. Scores on current motion sickness susceptibility screening questionnaires have been shown to correlate fairly well with an individual's ability to tolerate a provocative motion but better instruments are needed. Research focused on determining appropriate genetic, physiologic, psychological, and behavioral measures to further refine motion sickness susceptibility screening is necessary. For example, researchers have found that individuals who are more susceptible to motion sickness score higher on certain personality factors such as, neuroticism and anxiety, and lower on extraversion when compared to individuals who are less susceptible (Fox & Arnon, 1988; Gordon et al., 1991; Lentz & Collins, 1977). Stern and Koch (1996) reported a strong relationship between family history of motion sickness and a person's likelihood of being susceptible. Lentz and Collins (1977) examined behavioral variables such as alcohol consumption habits and found these factors to be correlated to an individual's level of susceptibility to varying degrees. Physiological variables such as cortisol levels, epinephrine, and norepinepherine have also been indicators of susceptibility to motion sickness (Stern & Koch, 1996). These research findings highlight the relationship among genetics, psychological and behavioral variables, physiological variables, and motion sickness susceptibility which may be useful in future endeavors for the development of a multi-factorial prediction battery.

Future studies could also benefit from the addition of plasma sampling, collected solely, or in conjunction with, saliva to establish better defined absorption profile of intranasal scopolamine and to establish the salivary/plasma relationship for scopolamine. Salivary sampling represents a relatively simple, non-invasive technique for monitoring drug levels. With more research this method may be feasible for use with oral and transdermal scopolamine, but is unlikely that valid and reliable drug concentrations can be obtained when using intranasal administration.

One final area for future study is the potential of using intranasal scopolamine for rescue. Numerous studies have assessed the efficacy of scopolamine, in one form or another as a prophylactic for motion sickness, but only one published study to date has explored the efficacy of IN SCOP after the onset of symptoms (Chinn et al., 1955). Because of intranasal scopolamine's rapid absorption profile, further investigation regarding its efficacy as a rescue therapy is warranted.

Intranasal Scopolamine Study Conclusions

These data suggest that intranasal delivery of scopolamine is a safe and practical alternative route of medication administration in dynamic military and space environments. The absorption rate of intranasal scopolamine proved superior to absorption rates for oral scopolamine, without causing significant cognitive decrement or increasing symptomotology, while overcoming administration challenges experienced with other delivery methods. Future studies should include plasma analysis of pharmacotherapeutic variables, motion sickness susceptibility screening, and methodological design changes.

Military Significance

With the implementation of Sea Power 21, and the concept of sea-basing in the military's future, motion sickness will become a greater problem, not only for Navy but for Army and Air Force personnel. The results from intranasal scopolamine studies suggest that this novel route of administration holds promise as a fast-acting, field expedient, motion sickness countermeasure. In addition to the U.S. military, the U.S. space program has been seeking a highly effective motion sickness countermeasure with the potential of rescue treatment. Initial pharmacotherapeutic data show great promise for action in less than 15 minutes. Future testing should concentrate on controlled laboratory tests, and then field testing, to confirm the operational value of intranasal scopolamine.

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Copyright Statement

References

Ahmed, S., Sileno, A. P., deMeireles, J.C., Dua, R., Pimplaskar, H. K., Xia, W. J, et al. (2000). Effects of pH and dose on nasal absorption of scopolamine hydrobromide in human subjects. *Pharmaceutical Research, 17*, 974-977.

Akerstedt. T. & Gillberg, M. (1990). Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience, 52*, 29-37.

Ambrose, M. R., Baggett, J. C., Baisden, A. G., Bason, R. B., Bercier, C. H., Berg, S. W., et al. (1991). *Flight Surgeon's Manual* (3rd ed.). Washington D.C.: The Bureau of Medicine and Surgery - Department of the Navy.

Bagian, J. P. (1991). First intramuscular administration in the U.S. Space Program. *Journal of Clinical Pharmacology, 31*, 920.

Bagian, J. P. & Ward, D. F. (1994). A retrospective study of promethazine and its failure to produce the expected incidence of sedation during space flight. *Journal of Clinical Pharmacology, 34*, 649-651.

Banks, R. D., Salisbury, D. A. & Ceresia, P. J. (1992). The Canadian Forces Airsickness Rehabilitation Program, 1981-1991. *Aviation, Space, and Environmental Medicine, 63*, 1098-1101.

Brand, J. J. (1970). A survey of recent motion sickness research. *Journal of the Royal Naval Medical Services, 56*, 204-207.

Brown, J. H. & Taylor, P. (2001). Muscarinic receptor agonists and antagonists. In J.G. Hardman, L.E. Limbird, and A.G. Gillman, (Eds.), *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*: *10 ed.* (p. 148-53). Europe: McGraw-Hill Education.

Chinn, H. I. (1951a). Motion Sickness. School of Aviation Medicine, Randolph AFB Special Report.

Chinn, H. I. (1951b). Motion sickness in the military service. *Military Medicine, 108*, 20-29.

Chinn, H. I., Milch, L. J. & Dugi, A.J. (1953). Comparison of various drugs against airsickness. *Journal of Applied Physiology, 6*, 257-259.

Chinn, H. I., Hyde, R. W. & Milch, L. J. (1955). Prevention and treatment of motion sickness by intranasal medication. *Proceedings of the Society for Experimental Biology and Medicine, 90*, 666-669.

Chinn, H. I & Smith, P. K. (1953). Motion sickness. *Pharmacology Review, 7*, 32-82.

Cornum, R. C., Caldwell, J., Cornum, K. (1997). Stimulant Use in Extended Flight Operations. *Airpower Journal, Spring*, 53-58.

Cowings, P.S., Stout, C.S., Toscano, W.B., Reynoso, S., DeRoshia, C. & Miller, N. E. (1996). *The effects of Promethazine on human performance, mood states, and motion sickness tolerance*. (Report No. NASA TM-108840). Moffett Field (CA): Ames Research Center.

Cowings, P. S., Toscano, W. B. & DeRoshia, C. (1998). *An Evaluation of the Frequency and Severity of Motion Sickness Incidences in Personnel Within the Command and Control Vehicle (C2V).* (Report No. NASA TM-112221). Moffett Field (CA): Ames Research Center.

Cowings, P. S., Toscano, W. B., DeRoshia, C. & Tauson, R. (1999). *Effects of Command and Control Vehicle (C2V) Operational Environment on Soldier Health and Performance.* (Report No. NASA TM-208786). Moffett Field (CA): Ames Research Center.

Davis, J. R., Vanderploeg, J. M., Santy, P. A., Jennings, R. T. & Stewart, D. F. (1988). Space motion sickness during 24 flights of the space shuttle. *Aviation, Space, and Environmental Medicine, 59,* 1185-1189.

Davis, J. R., Jennings, R. T., Beck, B. G. & Bagian, J. P. (1993). Treatment efficacy of intramuscular promethazine for space motion sickness. *Aviation, Space, and Environmental Medicine, 64,* 230-233.

Dobie, T. G. (1974). *Motion Sickness*. (AGARD-NATO; Report No; AGARD-AG-177). France: Neuilly-sur-Seine.

Dobie, T. G. & May, J. G. (1994). Cognitive-behavioral management of motion sickness. *Aviation, Space, and Environmental Medicine, 65,* C1-C2.

Ebert, U., Siepmann, M., Oertel, R., Wesnes, K. A. & Kirch, W. (1998). Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *Journal of Clinical Pharmacology, 38,* 720-726.

Elsmore, T. F. & Reeves, D.L. (2004). ANAM readiness evaluation system (ARES): User's guide. *Activity Research Services*.

Elsmore, T. F., Reeves, D. L. & Reeves, A. N. (2007). The ARES test system for palm OS handheld computers. *Archives of Clinical Neuropsychology, 22 Suppl 1,* S135-144.

Estrada, A., LeDuc, P. A., Curry, I. P., Phelps, S. E. & Fuller, D. R. (2007). Airsickness prevention in helicopter passengers. *Aviation, Space, and Environmental Medicine, 78,* 408- 413.

Fatah, A. & Cohn, J. P. (2003). Saliva as an Alternate to Urine and Blood. *Corrections Today, 65*.

Fox, S. & Arnon, I. (1988). Motion sickness and anxiety. *Aviation, Space and Environmental Medicine, 59,* 728-33.

Fung, G., Ho, T., Lee, S., Manaretto, J., & Tsai, C. (2003).Transdermal scopolamine drug delivery systems for motion sickness. Retrieved August 14, 2007, from: http://hdl.handle.net/1813/141

Golding, J. F. & Stott, J. R. (1997). Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance, and heart rate. *British Journal of Clinical Pharmacology, 43*, 633-637.

Golding, J. F. (2003, May). *A short questionnaire to assess motion sickness susceptibility (MSSQ-Short): Normative values, reliability, and predictive validity.* Paper presented at the XXXVII International Symposium of Otoneurology, Saint-Entienne, France.

Golding, J. F. (2006). Motion sickness susceptibility. *Autonomic Neuroscience, 129*, 67-76.

Gordon, C. R., Mankuta, D., Shupak, A., Spitzer, O., & Doweck, I. (1991). Recurrent classic migraine attacks following transdermal scopolamine intoxication. *Headache, 31*, 172-174.

Haeckel, R. (1993). Factors influencing the saliva/plasma ratio of drugs. *The Annals of the New York Academy of Sciences, 694*, 128-142.

Heer, M. & Paloski, W. H. (2006). Space motion sickness: incidence, etiology, and countermeasures. *Autonomic Neuroscience, 129*, 77-79.

Hixson, W. C., Guedry, F. E. & Lentz, J. M. (1984). *Results of a longitudinal study of airsickness incidence during naval flight officer training*. (AGARD-NATO Report No. AD-A150887). France: Neuilly-sur-Seine.

Hixon, W. C. & Niven, J. I. (1969). Directional differences in visual acuity during vertical nystagmus. (NAMI-1079 NASA Order No. R-93). Pensacola, FL: Naval Aerospace Medical Institute.

Homick, J. L., Kohl, R. L., Reschke, M. F., Degioanna, J. & Cintron-Trevino, N. M. (1983). Transdermal scopolamine in the prevention of motion sickness: Evaluation of the time course of efficacy. *Aviation, Space, and Environmental Medicine, 54*, 994-1000.

Hutchins, C. W., Jr. & Kennedy, R. S. (1965). Clinical problems in aviation medicine. Relationship between past history of motion sickness and attrition from flight training. *Aerospace Medicine, 36*, 984-987.

Hyde, R. W., Tonndorf, J. & Chinn, H. I. (1953). Absorption from the nasal mucous membrane. *Annals of Otology, Rhinology, and Laryngology, 62*, 957-968.

Jones, D. R., Levy, R. A., Gardner, L., Marsh, R. W., & Patterson, J. C. (1985). Self-control of psychophysiology response to motion stress: using biofeedback to treat airsickness. *Aviation, Space, and Environmental Medicine, 56*, 1152-1157.

Jusko, W. J. & Milsap, R. L. (1993). Pharmacokinetic principles of drug distribution in saliva. *The Annals of the New York Academy of Sciences, 694*, 36-47.

Kane, R. L., Roebuck-Spencer, T., Short, P., Kabat, M. & Wilken, J. (2007). Identifying and monitoring cognitive deficits in clinical populations using Automated Neuropsychological Assessment metrics (ANAM) tests. *Archives of Clinical Neuropsychology, 22 Suppl* 1, S115-S126.

Kanto, J., Kentala, E., Kaila, T. & Pihlajamaki, K. (1989). Pharmacokinetics of scopolamine during caesarean section: Relationship between serum concentration and effect. *Acta-Anaesthesiol-Scand, 33*, 482-486.

Klocker, N., Hanschke, W., Toussaint, S. & Verse, T. (2001). Scopolamine nasal spray in motion sickness: a randomized, controlled, and crossover study for the comparison of two scopolamine nasal sprays with oral dimenhydrinate and placebo. *European Journal of Pharmaceutical Sciences, 13*, 227-232.

Langman, L. J. (2007). The use of oral fluid for therapeutic drug management. *The Annals of the New York Academy of Sciences, 1098,* 145-166.

Lentz, J. M. & Collins, W. E. (1977). Motion sickness susceptibility and related behavioral characteristics in men and women. *Aviation, Space, and Environmental Medicine, 48*, 316-22.

Lewandowski, A. G., Dietz, A. J. & Reeves, D. L. (1997). A neuropsychologic-pharmacodynamic paradigm for demonstrating cognitive enhancement and suppression in the elderly. *Archives of Internal Medicine, 157,* 2350-2356.

Magerl, H. & Schulz, E. (2007). *Methods of Saliva Analysis and the Relationship between Saliva and Blood Concentration*. Retrieved October 22, 2007, from http://www.druglibrary.org/schaffer/MISC/driving/s3p1.htm

Marcus, D. A. & Furman, J. M. (2006). Prevention of motion sickness with rizatriptan: a double-blind, placebo-controlled pilot study. *Medical Science Monitor, 12*, I1-I7.

Money, K. E. (1970). Motion sickness. *Physiological Reviews, 50*, 1-39.

Nachum, Z., Shahal, B., Shupak, A., Spitzer, O., Gonen, A., Beiran, I., et al. (2001). Scopolamine bioavailability in combined oral and transdermal delivery. *The Journal of Pharmacology and Experimental Therapeutics, 296*, 121-123.

Navazesh, M. (1993). Methods for collecting saliva. *Annals of the New York Academy of Sciences, 694*, 72-77.

Neely, J. C. (1956). The R.A.F. near-point rule. *British Journal Ophthalmology, 40*, 636-637.

Parrott, A. C. (1986). The effects of transdermal scopolamine and four dose levels of oral scopolamine (0.15, 0.3, 0.6, and 1.2 mg) upon psychological performance. *Psychopharmacology (Berl*), *89*, 347-354.

Parrott, A. C. (1989). Transdermal scopolamine: a review of its effects upon motion sickness, psychological performance, and physiological functioning. *Aviation, Space, and Environmental Medicine, 60*, 1-9.

Pethybridge, R. J. (1982). *Sea sickness incidence in royal navy ships*. (Report No. INM 37/82). Gosport, England: Institute of Naval Medicine.

Putcha, L., Cintron, N. M., Tsui, J., Vanderploeg, J. M. & Kramer, W. G. (1989). Pharmacokinetics and oral bioavailability of scopolamine in normal subjects. *Pharmaceutical Research*, 6, 481-485.

Putcha, L., Tietze, K. J., Bourne, D. W., Parise, C. M., Hunter, R. P. & Cintron, N. M. (1996). Bioavailability of intranasal scopolamine in normal subjects. *Journal of Pharmaceutical Sciences, 85*, 899-902.

Putcha, L. (1999). Pharmacotherapeutics in space. *Journal of Gravitational Physiology, 6*, 165-168.

Reeves, D. L., Winter, K. P., Bleiberg, J., & Kane, R. L. (2007). ANAM® genogram: Historical perspectives, description, and current endeavors. *Archives of Clinical Neuropsychology, Suppl. 22*, S15- S37.

Renner, U. D., Oertel, R. & Kirch, W. (2005). Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Therapeutic Drug Monitoring*, 27, 655-665.

Reschke, M. F., Bloomberg, J. J., Harm, D. L., Paloski, W. H., Layne, C. & McDonald, V. (1998). Posture, locomotion, spatial orientation, and motion sickness as a function of space flight. *Brain Research Reviews*, 28, 102-117.

Rickert, D. (2000). *C41 Mobile Operational Prototype (CMOP). User Jury 8 Summary, Report, September 19-21, 2000*. Woodbridge, VA: General Dynamics Amphibious Systems.

Royal, L., Jessen, B. & Wilkins, M. (1984). Motion sickness susceptibility in student navigators. *Aviation, Space, and Environmental Medicine, 55*, 277-280.

Ryback, R. S., Rudd, R. E., Matz, G. J. & Jennings, C. L. (1970). Motion sickness in USAF flying personnel. *Aerospace Medicine, 41*, 672-677.

Schipani, S. P., Bruno, R. S., Lattin, M. A., King, B. M. & Patton, D. J. (1998). *Quantification of Cognitive Process Degradation While Mobile, Attributable to the Environmental Stressors Endurance, Vibration, and Noise*. (Apr. Report No. ARL-TR-1603). Aberdeen Proving Ground, MD: Army Research Laboratory.

Simmons, R. G., Phillips, J. B., Lojewski, R. A., Lawson, B. D., & Putcha, L. (2008). The efficacy of dextroamphetamine as a motion sickness countermeasure for use in military operational environments. Pensacola, Naval Aerospace Medical Research Laboratory. (Report #08-09)

Stern, R. M. & Koch, K. L. (1996). Motion sickness and differential susceptibility. *Current Directions in Psychological Science, 5*, 115-119.

Stevens, S. C. & Parsons, M. G. (2002). Effects of motion at sea on crew performance: A Survey. *Marine Technology Society, 39*, 29-47.

Tonndorf, J., Hyde, R. W., Chinn, H. I. & Lett, J. E. (1953). Absorption from nasal mucous membrane: systemic effect of hyoscine following intranasal administration. *The Annals of Otology, Rhinology, and Laryngology, 62*, 630-641.

Wilken, J. A., Sullivan, C. L., Lewandowski, A. & Kane, R. L. (2007). The use of ANAM to assess the side-effect profiles and efficacy of medication. *Archives of Clinical Neuropsychology, 22 Suppl 1*, S127-133.

Wilkinson, J. A. (1987). Side effects of transdermal scopolamine. *The Journal of Emergency Medicine, 5*, 389-392.

Wood, C. D. & Graybiel, A. (1968). Evaluation of sixteen anti-motion sickness drugs under controlled laboratory conditions. *Aerospace Medicine, 39*, 1341-1344.

Wood, C. D., Graybiel, A., McDonough, R. G. & Kennedy, R. S. (1965). *Evaluation of some antimotion sickness drugs on the slow rotation room (No. 1).* (Report No. NSAM-922). Pensacola, FL: Naval School of Aviation Medicine.

Table 1. Descriptive Statistics for IN SCOP, PO SCOP and Placebo

Group	n	Male/ Female	Age	Weight (kg)	Height (cm)	BMI	MSSQ
IN SCOP	18	16/2	23.5	78.9	175.8	24.0	5.8
PO SCOP	18	17/1	23.9	80.8	177.0	24.4	3.2
Placebo	18	17/1	23.4	86.2	180.6	26.1	3.6
Total	54	50/4	23.4	82.1	177.8	24.8	4.1

Note. IN SCOP = Intranasal Scopolamine; PO SCOP = Oral Scopolamine; BMI = Body Mass Index; MSSQ = Motion Sickness Susceptibility Questionnaire- Short Form

Table 2. Estimated Marginal Means for Head Movements using the MSSQ-Short as a Covariate for IN SCOP, PO SCOP and Placebo

	Mean Head Movements
IN SCOP	255 ± 27.17
PO SCOP	238 ± 26.90
Placebo	210 ± 28.13

Table 3. Group Comparisons of Means and Standard Errors of Visual Accommodation and Subjective Sleepiness for IN SCOP, PO SCOP and Placebo.

	Time					
	1	2	3	4	5	6
VA_{IN}	13.12 ± 0.97	12.47 ± 0.68	12.94 ± 0.71	13.18 ± 0.82	13.06 ± 0.83	12.88 ± 0.76
VA_{PO}	14.67 ± 0.54	14.72 ± 0.54	16.89 ± 1.05	15.83 ± 0.76	15.00 ± 0.73	15.00 ± 0.76
VA_{P}	11.59 ± 0.50	12.11 ± 0.57	12.71 ± 0.75	12.65 ± 0.87	12.00 ± 0.68	11.59 ± 0.64
KSS_{IN}	4.5 ± 0.44	3.83 ± 0.42	4.39 ± 0.47	4.44 ± 0.44	4.89 ± 0.48	4.61 ± 0.54
KSS_{PO}	3.56 ± 0.44	3.06 ± 0.22	3.06 ± 0.41	3.44 ± 0.42	3.33 ± 0.43	3.33 ± 0.29
KSS_{P}	3.94 ± 0.42	3.33 ± 0.29	3.44 ± 0.36	3.17 ± 0.35	3.06 ± 0.37	3.50 ± 0.32

Note. VA = Visual Accommodation (in centimeters) and KSS = Karolinska Sleepiness Scale. For VA, Times 1-6 correspond with baseline and 10, 70, 95, 120, & 140 minutes post-IN dose and baseline, 55, 115, 140, 165, 185 minutes post-PO dose. Times 1-6 for KSS scores are baseline, 15, 70, 105, 125, & 150 minutes post-IN dose and baseline, 60, 115, 150, 170 & 195 minutes post-PO dose.

Table 4. Group Comparisons of Means and Standard Errors for the ARES Cognitive Battery for IN SCOP, PO SCOP and Placebo

	Time				
	1	2	3	4	5
SRT_{IN}	218.06 ± 4.92	211.61 ± 4.98	217.50 ± 4.55	208.44 ± 6.23	212.61 ± 5.08
SRT_{PO}	212.06 ± 4.80	217.59 ± 5.92	208.71 ± 5.01	203.82 ± 6.48	212.65 ± 8.95
SRT_{P}	219.28 ± 6.18	220.56 ± 7.34	223.00 ± 5.65	215.33 ± 5.35	211.33 ± 5.7
RM_{IN}	418.44 ± 14.50	410.69 ± 14.30	401.25 ± 14.43	429.31 ± 18.47	420.13 ± 16.33
RM_{PO}	420.39 ± 16.02	417.06 ± 12.08	412.89 ± 13.15	414.39 ± 12.53	415.22 ± 10.75
RM_{P}	423.17 ± 16.99	418.44 ± 15.12	411.17 ± 14.22	420.50 ± 14.44	417.94 ± 14.64
MS_{IN}	1102.50 ± 74.25	1045.56 ± 72.27	1435.28 ± 110.02	1068.83 ± 94.29	1281.83 ± 105.23
MS_{PO}	942.00 ± 65.27	1029.61 ± 72.64	1127.39 ± 67.11	971.17 ± 63.03	1120.94 ± 68.89
MS_{P}	886.06 ± 67.57	901.11 ± 51.20	1131.83 ± 88.70	877.44 ± 91.31	897.33 ± 49.49
LR_{IN}	1539.44 ± 111.66	1579.56 ± 126.84	1558.00 ± 124.39	1643.22 ± 134.01	1555.67 ± 120.65
LR_{PO}	1557.61 ± 95.46	1531.00 ± 87.05	1490.72 ± 88.07	1522.28 ± 100.39	1496.11 ± 99.02
LR_{P}	1399.50 ± 84.69	1336.00 ± 74.61	1360.94 ± 85.87	1402.67 ± 74.19	1378.44 ± 71.80

Note. All scores in milliseconds. IN SCOP = Intranasal Scopolamine; PO SCOP = Oral Scopolamine. SRT = Simple Reaction Time, RM = Running Memory, MS = Matching to Sample, LR= Logical Reasoning, $_{IN}$ = Intranasal scopolamine, $_{PO}$ = Oral Scopolamine, and $_{P}$ = Placebo. Times 1-5 correspond with Baseline and 10, 95, 120 & 140 minutes post-IN SCOP dose, and Baseline and 55, 140, 165, & 185 minutes post-PO SCOP dose, respectively.

Table 5. [2] Summary of Scopolamine Saliva Estimates for IN SCOP, PO SCOP and Placebo

		0.4 mg IN SCOP		0.8 mg PO SCOP	
	Units	Mean	SD	Mean	SD
Tlag	h	0.014	0.059	0.563	1.006
Tmax	h	1.463	0.980	2.792	0.803
Cmax	ng/mL	54.857	103.739	0.361	0.348
t ½ Lambda z	h	0.842	0.876	2.643	1.432
AUClast	ng*h/mL	51.732	93.802	0.459	0.409
BE(last)	%			0.440	

Note. BE = bioequivalence: calculated as (AUClast po/D po)/(AUClast in/ D in); IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine, AUC = area under the curve, D = dose.

[2] All values provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX

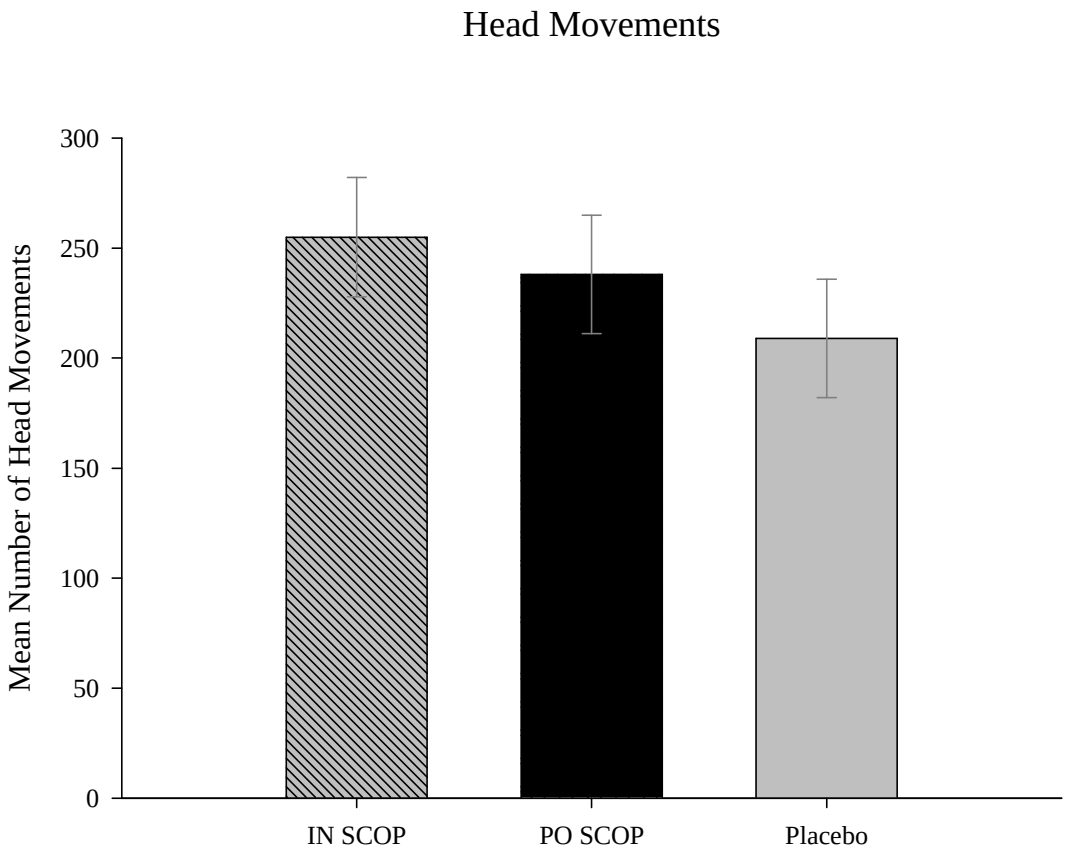
Table 6. [3] Concentration Levels of Intranasal and Oral Scopolamine

	Time Post-IN SCOP (hours)					
Subject Number	0	0.25	1.25	1.5	1.9	2.75
4	0	6.426	3.419	2.105	3.677	7.283
13	0	0.071	0.109	0.267	0.203	0.318
15	0	0.238	0.795	0.743	0.945	1.101
20	0	0.257	0.412	0.330	0.125	0.205
23	0	5.917	2.123	1.879	1.589	1.067
31	0	1.307	6.629	8.590	12.321	3.143
33	0	5.472	53.234	20.465	11.592	2.528
47	0	34.624	17.753	8.355	4.299	2.030
48	0	0.060	0.343	0.279	1.108	1.416
59	0	7.626	2.721	1.589	1.218	0.665
65	0	0	0.341	0.074	0.202	0.114
66	0	1.999	1.701	1.352	0.368	0.327
67	0	8.561	66.829	37.332	4.174	1.503
68	0	375.161	74.936	71.400	44.801	11.553
69	0	0.048	0.290	0.360	0.248	1.552
70	0	0.083	4.541	1.296	0.662	0.107
71	0	7.210	21.646	83.354	172.250	19.174
72	0	17.677	240.492	75.966	43.253	17.021
	Time Post-PO SCOP (hours)					
Subject Number	0	1	2	2.25	2.67	3.5
8	0	0	0.100	0.137	0.132	0.138
10	0	0	0.252	0.253	0.158	0.122
14	0	0.030	0.033	0.041	0.033	0.153
16	0	0	0	0	0.073	0.076
22	0	0	0	0	0.297	0.267
25	0	0	0	0	0.077	0.188
28	0	0	0	0	0.073	0.221
29	0	0.080	0.043	0.120	0.096	0.118
34	0	0.070	0.126	0.129	0.070	0.091
37	0	0.524	1.282	0.773	0.392	0.538
41	0	0.500	0	0	0	0.251
49	0	0.081	0.148	0.096	0.086	0.049
50	0	0.112	0.506	0.357	0.807	1.339
51	0	0.061	0.686	0.596	0.339	0.483
52	0	0.064	0.186	0.104	0.178	0.865
55	0	0.033	0.188	0.227	0.345	0.529
61	0	0	0	0	0	0

Note: All values are ng/mL; IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine

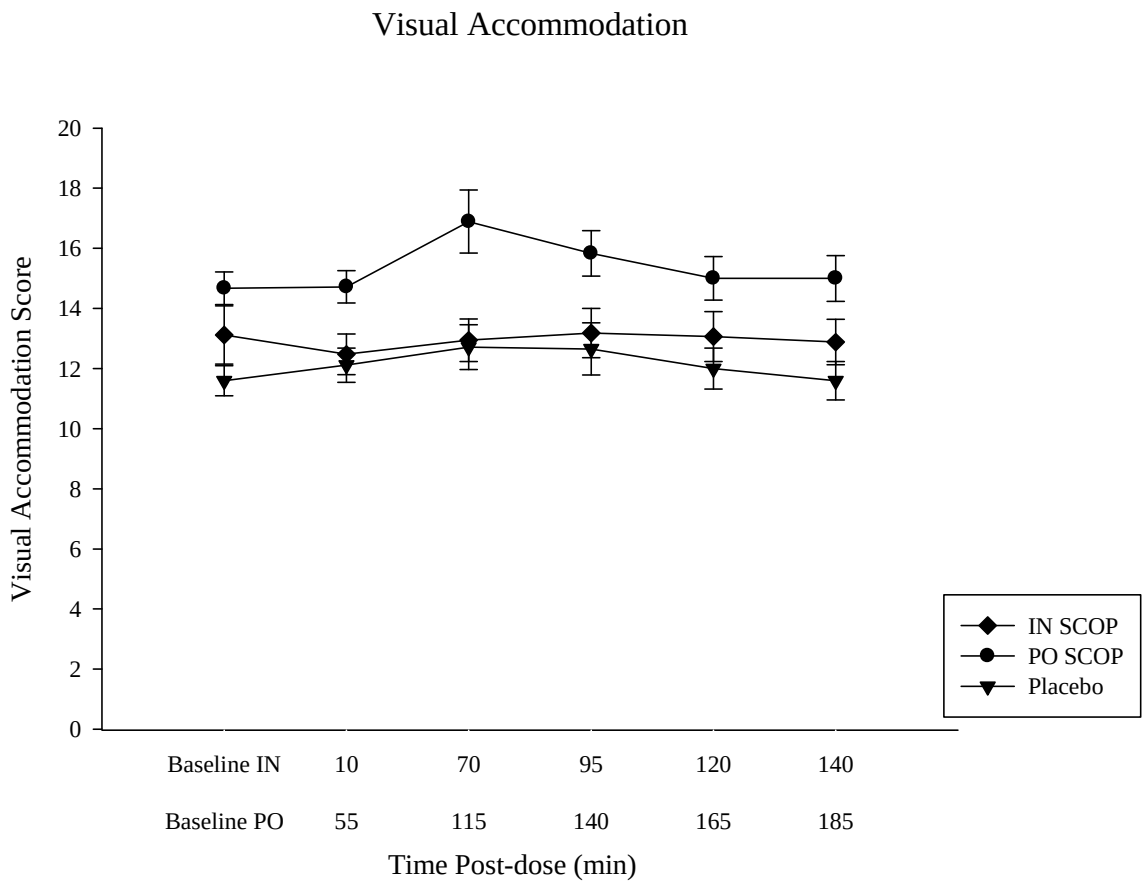
[3] All values provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX

Figure 1. Number of Head Movements (Estimate Marginal Means) to Moderate Nausea for IN SCOP, PO SCOP and Placebo



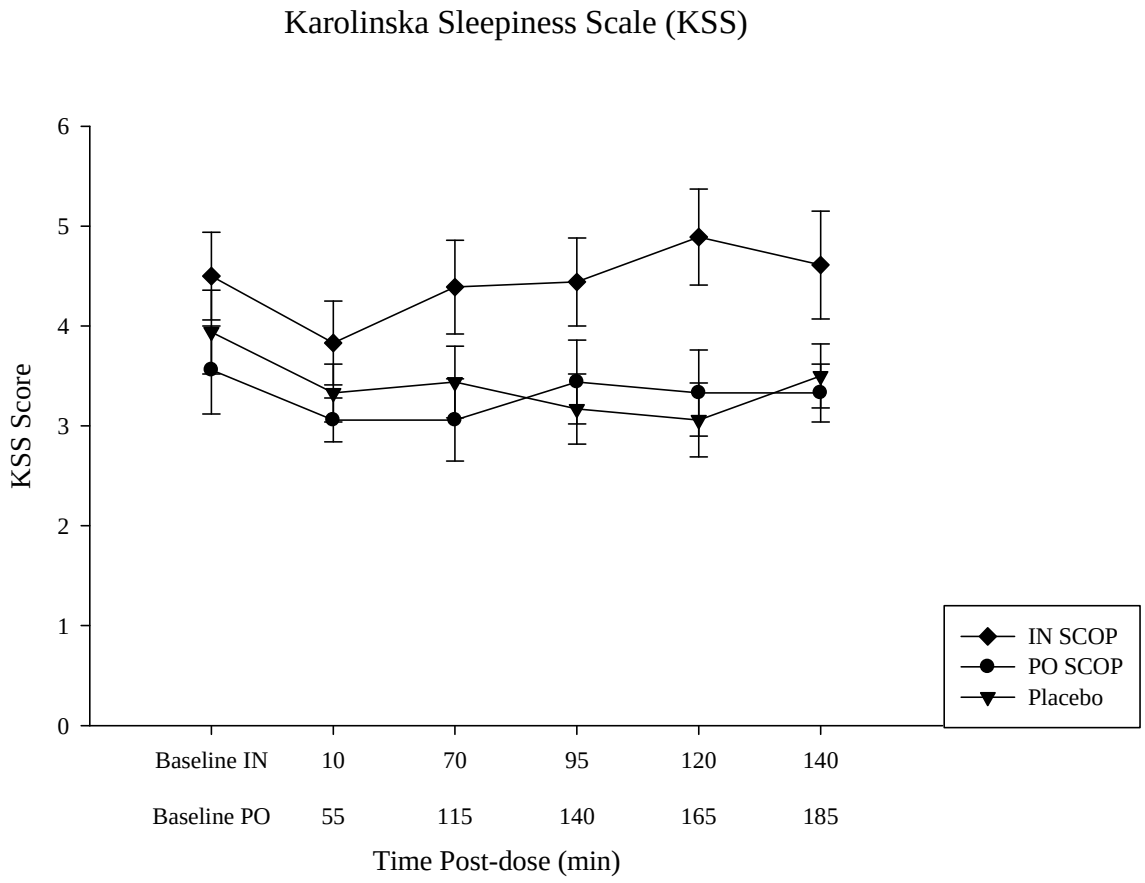
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant difference in head movements tolerated among the three groups (p>0.05).

Figure 2. Visual Accommodation Scores for IN SCOP, PO SCOP and Placebo Over Six Observations



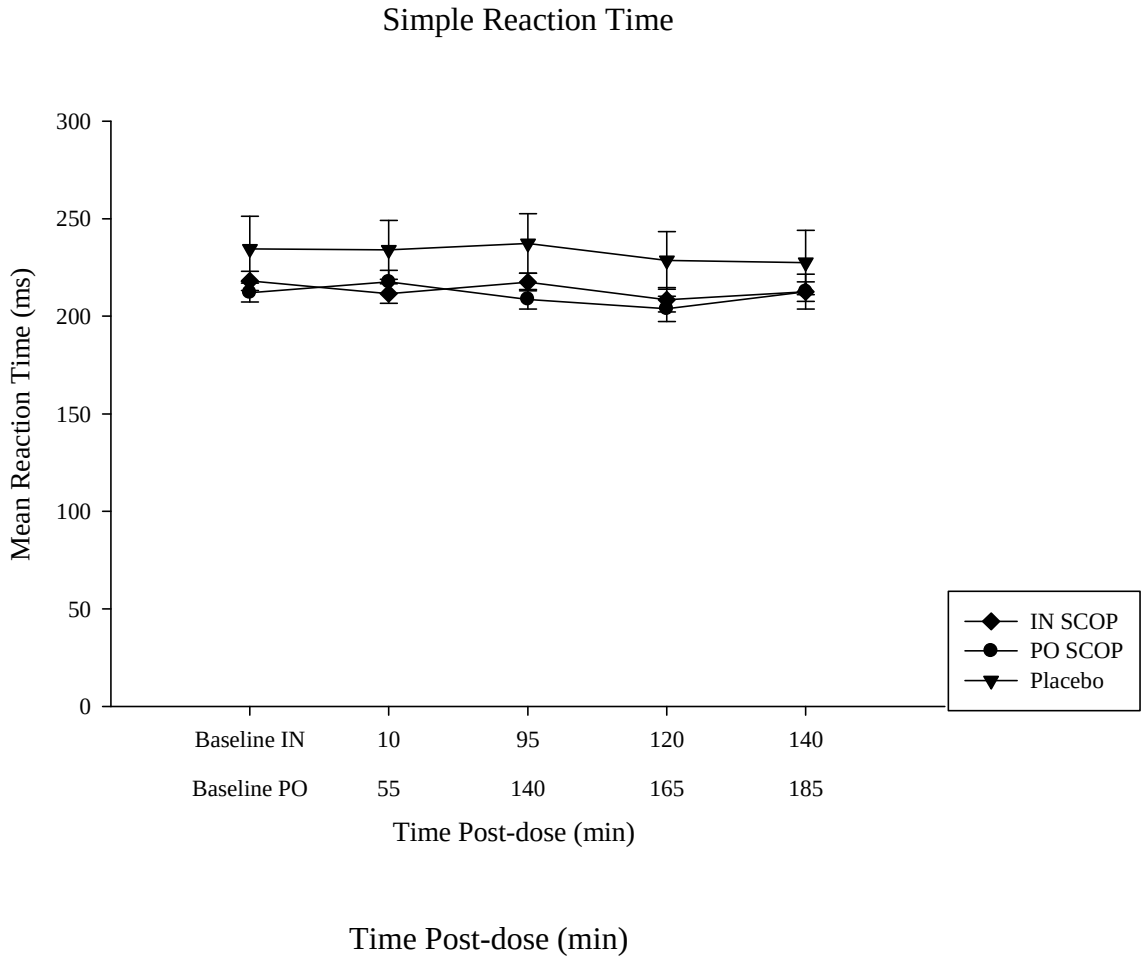
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant differences in VA scores among the three group over time (p>0.05).

Figure 3. Karolinska Sleepiness Scale Scores For IN SCOP, PO SCOP and Placebo Over Six Observations



Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant difference in KSS scores over time among the three groups (p>0.05).

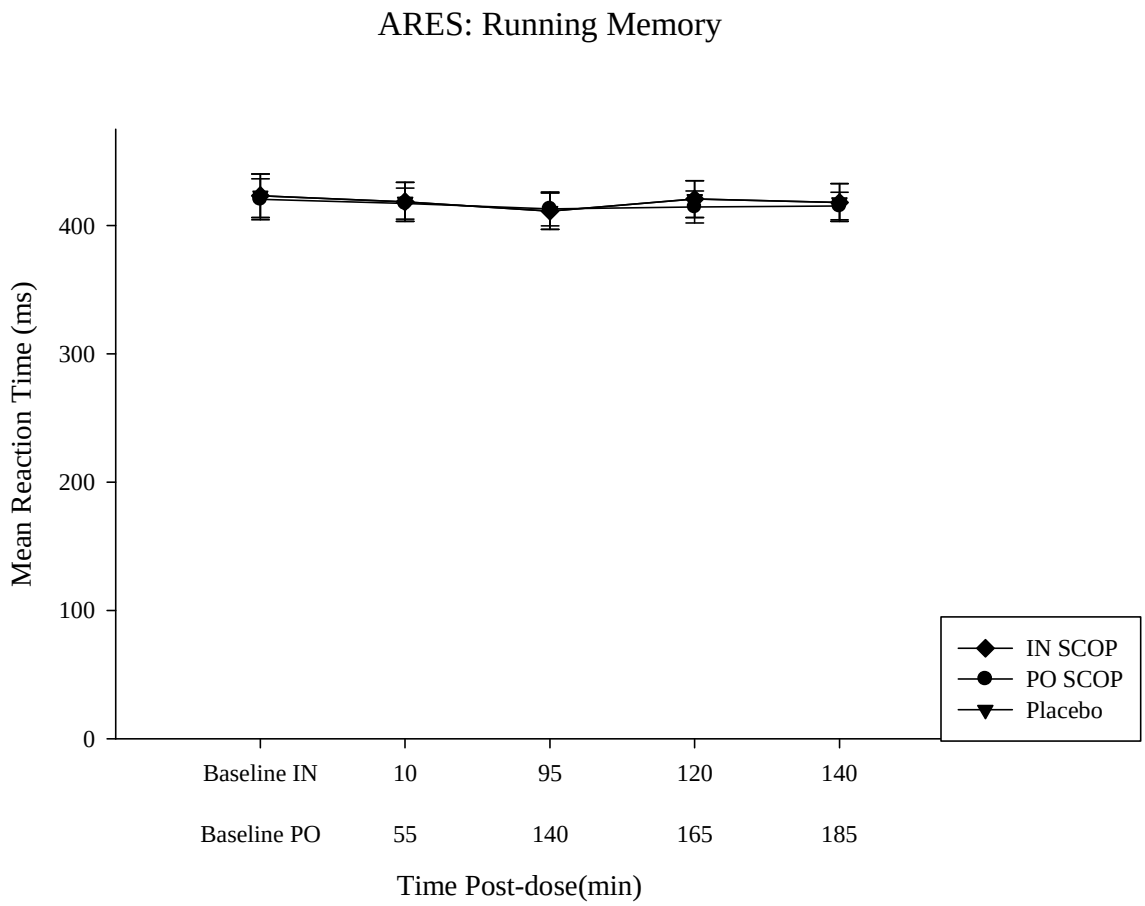
Figure 4. ARES Simple Reaction Time Scores for IN SCOP, PO SCOP and Placebo Over Five Observations



Time Post-dose (min)

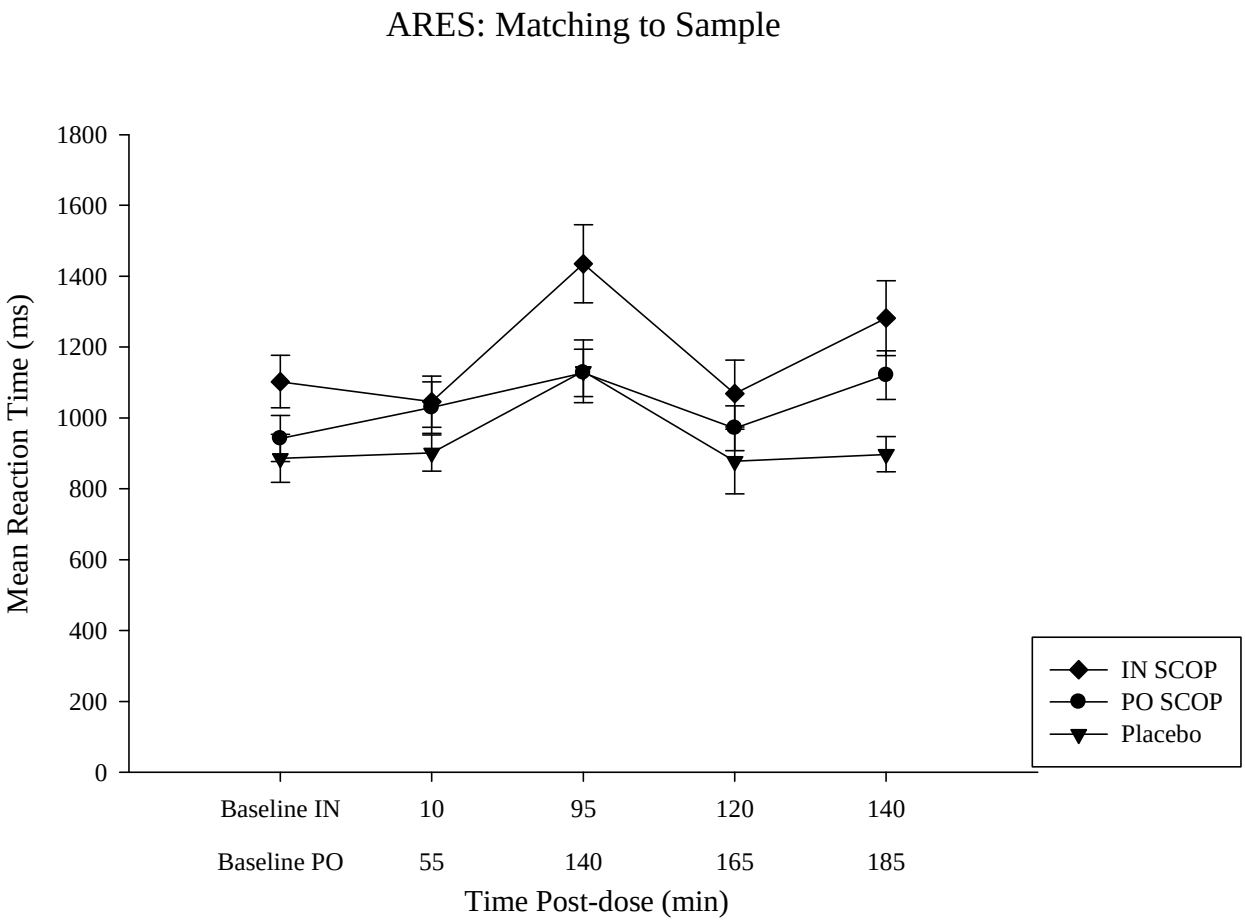
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant difference in ARES SRT scores over time among the three groups (p>0.05).

Figure 5. ARES Running Memory Scores for IN SCOP, PO SCOP and Placebo over Five Observations



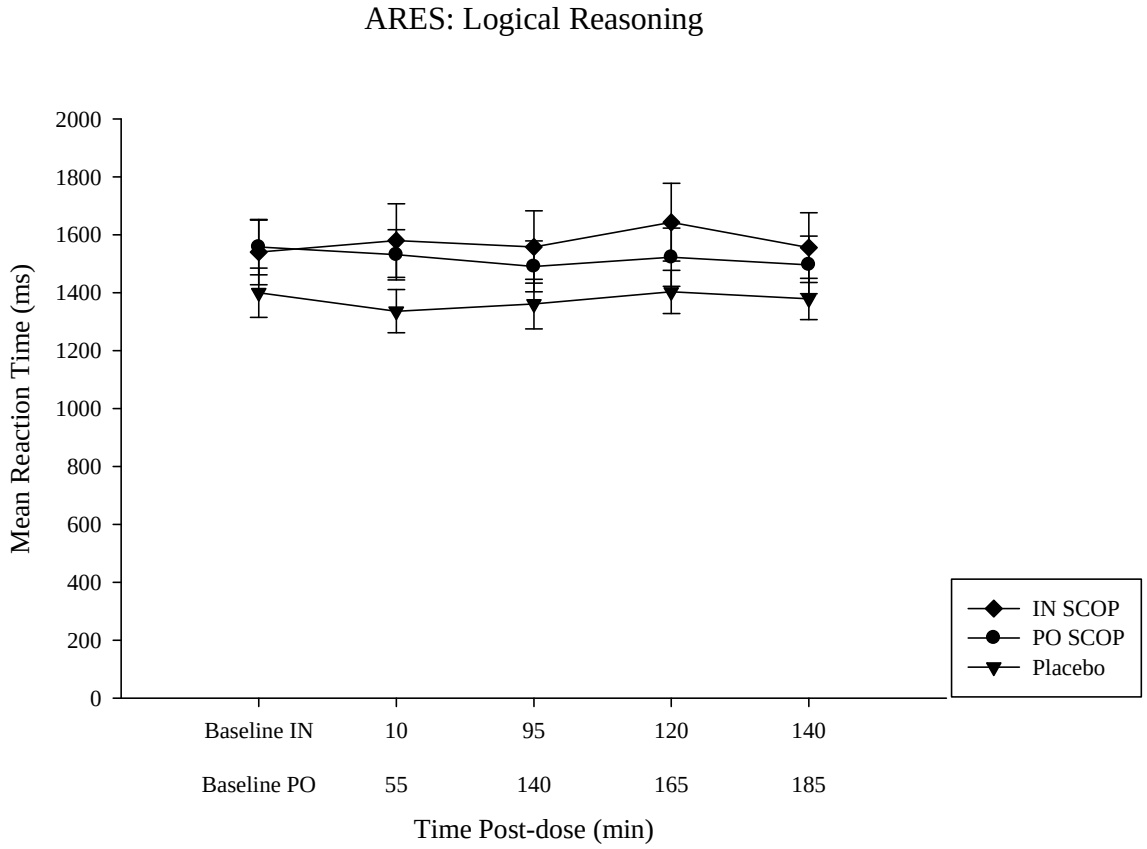
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant difference in ARES RM scores over time among the three groups (p>0.05).

Figure 6. ARES Matching to Sample Scores for IN SCOP, PO SCOP and Placebo over Five Observations



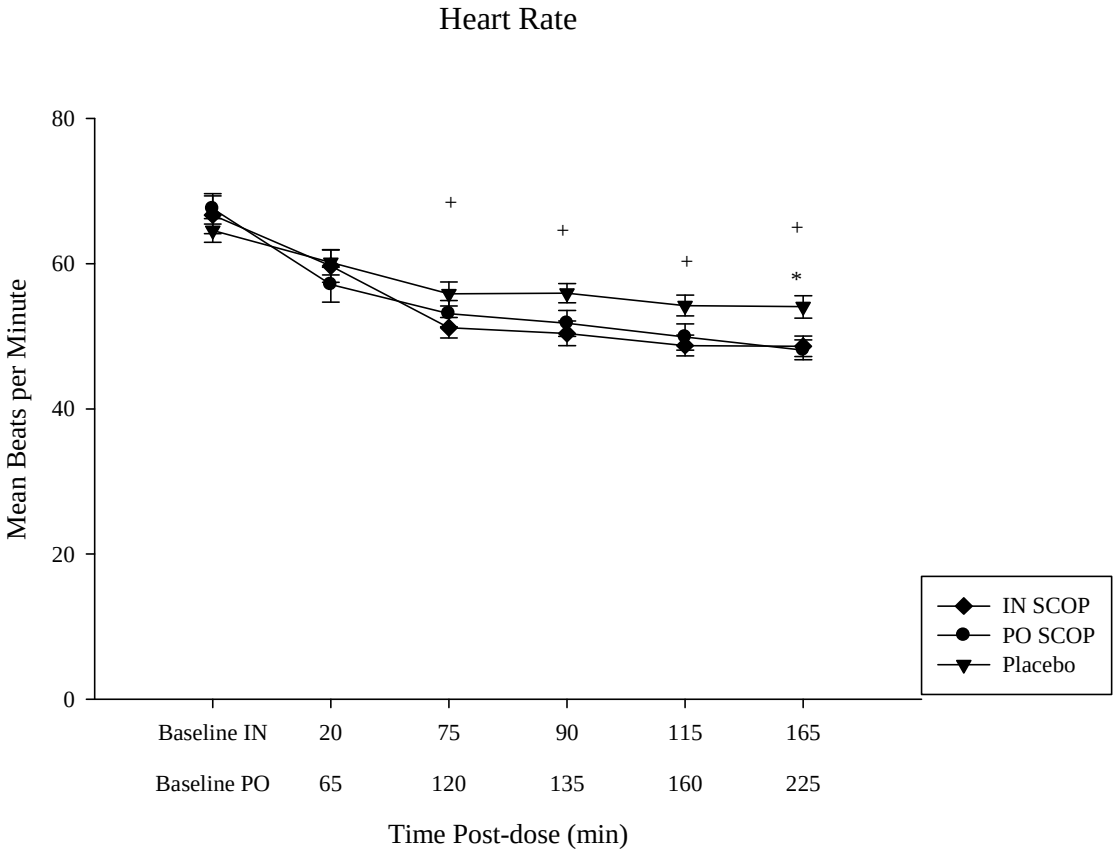
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant difference in MTS scores over time among the three groups (p>0.05).

Figure 7. ARES Logical Reasoning Scores for IN SCOP, PO SCOP and Placebo over Five Observations



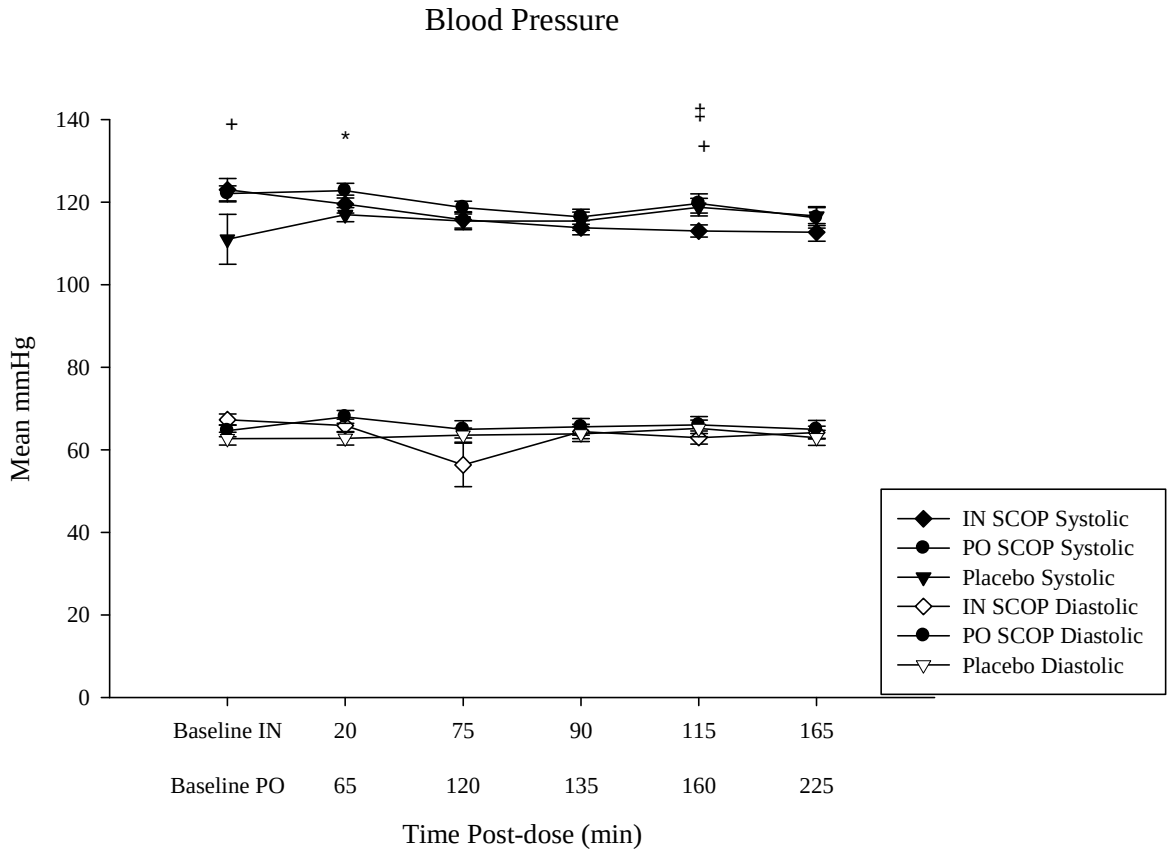
Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine. No significant differences in LR scores over time among the three groups (p>0.05).

Figure 8. Heart Rate Changes Over Time for IN SCOP, PO SCOP and Placebo



Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine; Significant group differences between IN SCOP and Placebo (+) at 75/120, 90/135, 115/160 and 165/225 minutes post-dose and differences between PO SCOP and Placebo (*) at 225 post-dose, (+,* = p <0.05).

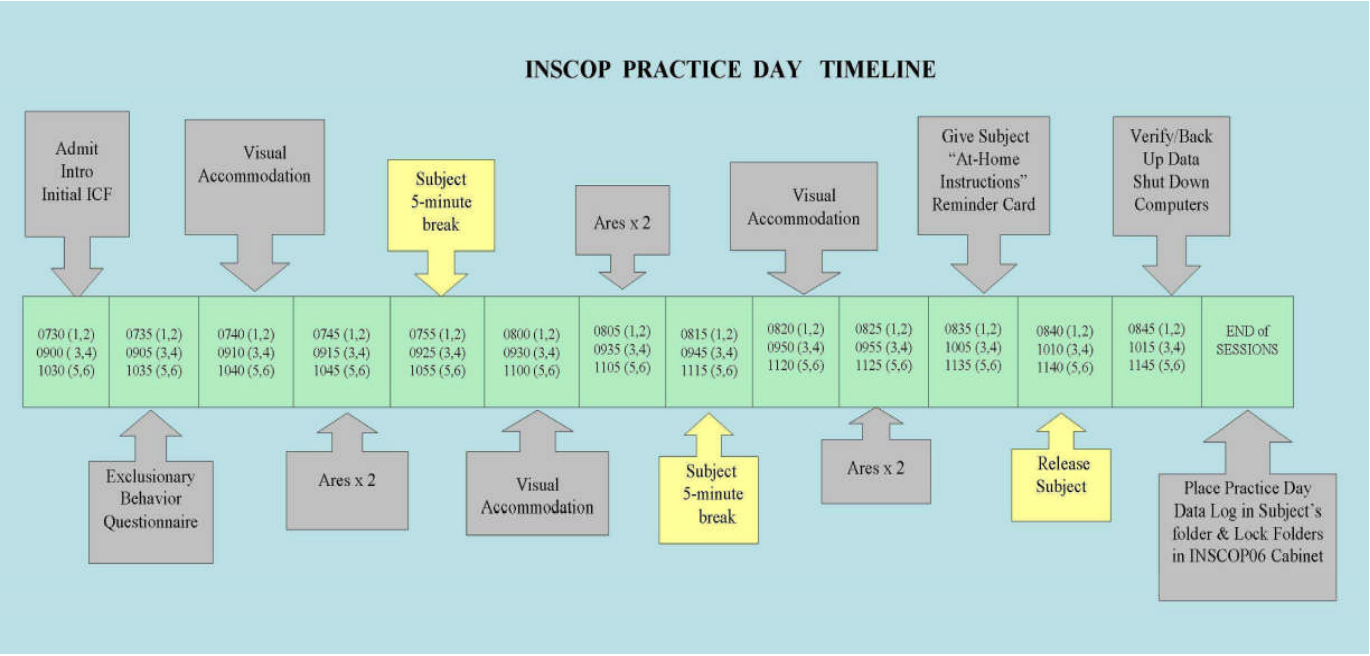
Figure 9. Change in Blood Pressure over Time for IN SCOP, PO SCOP and Placebo



Note. IN SCOP = Intranasal Scopolamine, PO SCOP = Oral Scopolamine; Significant group differences between IN SCOP and Placebo (+) for systolic blood pressure at baseline and 115/160 minutes post-dose, between PO SCOP and Placebo (*) at 65 minutes post-dose, and between IN SCOP and PO SCOP (‡) at 115/160 post-dose (+,*, ‡ = $p<0.05$).

Appendix 1. Picture of Human Disorientation Device

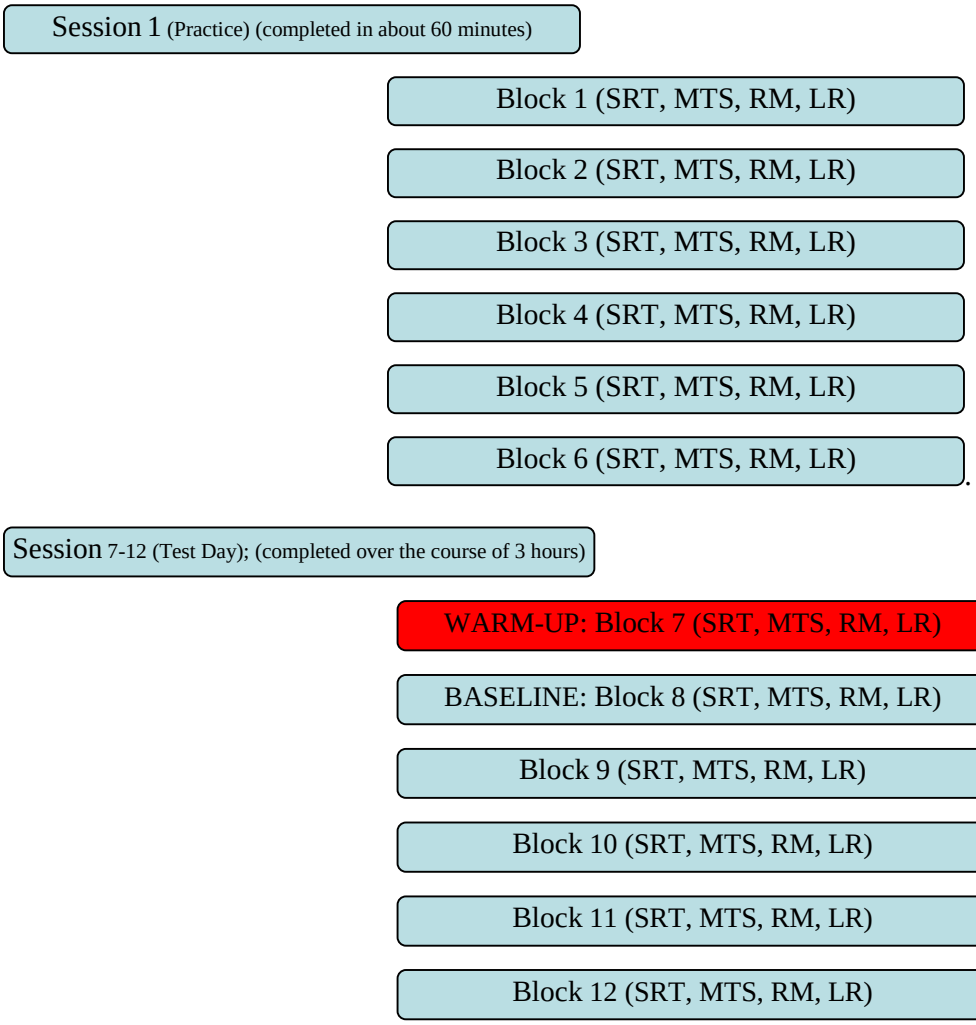
Appendix 2. Practice Day Timeline



Appendix 3. ARES Administration

I. Description of the Administration of the ARES Cognitive Battery

There were 2 testing sessions of the ARES Cognitive Battery for each subject. Both sessions contained 6 blocks of testing.



<u>Each Block consists of 4 tests (given in the same order each session):</u>

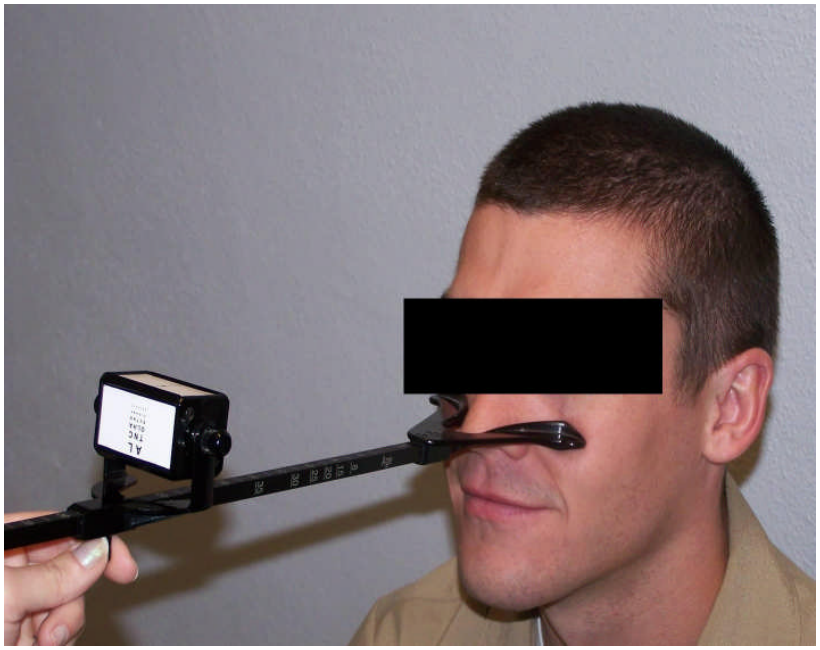
Simple Reaction Time - number of stimuli and time varied, and involved 15-20 stimuli (*) for approximately 30-40 seconds.

Matching To Sample - involved 10 stimuli (varied sequence) and lasted approximately 100-115 seconds (depending on reaction time).

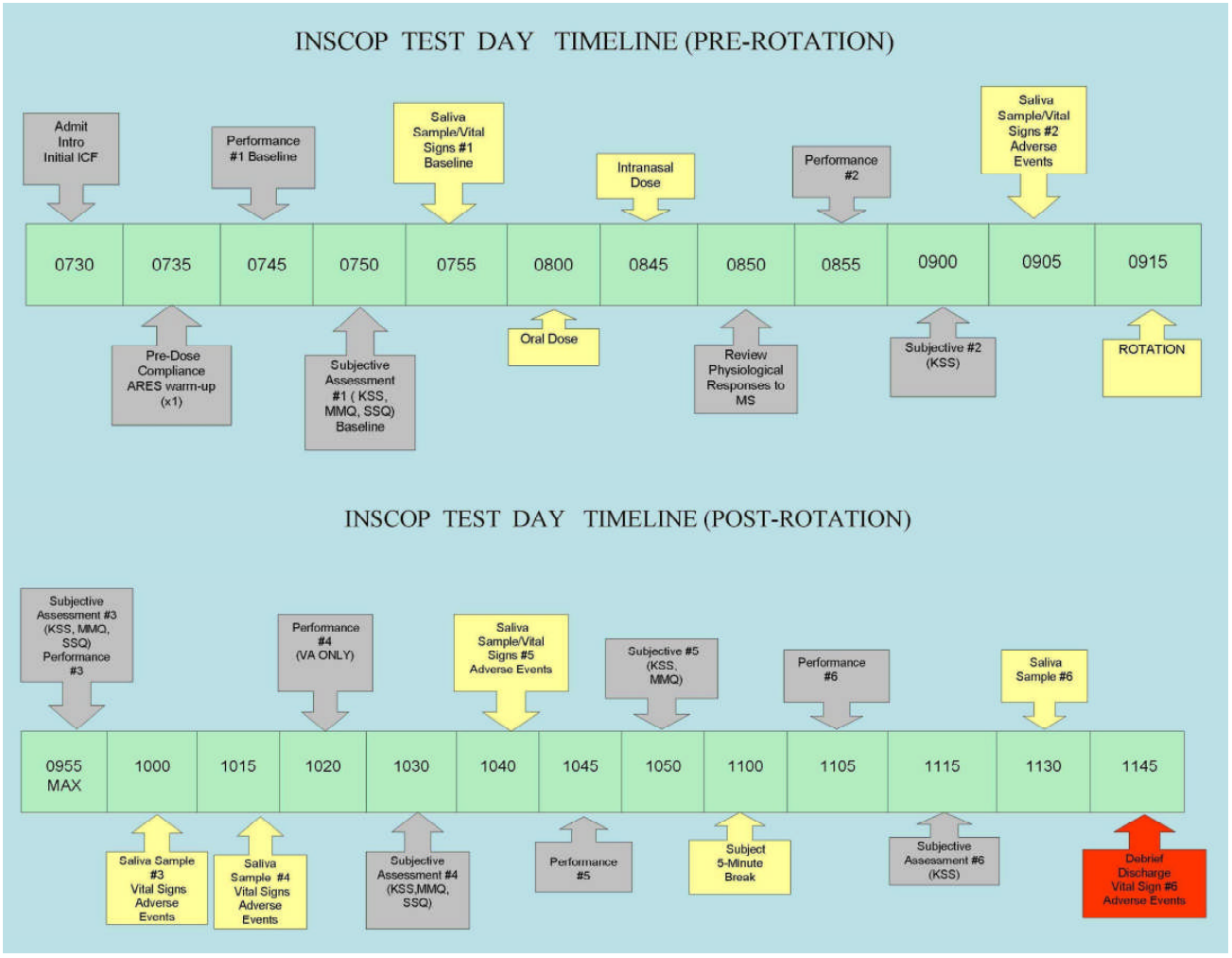
Running Memory - generally has 80 stimuli (varied sequence), unless the reactions times were “slow”, and then it decreased to 78 or 79. Times ranges from 130 to 160 seconds.

Logical Reasoning - involved 24 stimuli (varied sequence) and lasted approximately 60 to 90 seconds.

Appendix 4. RAF Rule



Appendix 5. Test Day Timeline



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14. ABSTRACT

Results from preliminary studies indicate intranasal scopolamine (IN SCOP) has faster absorption, higher bioavailability, and a more reliable therapeutic index than equivalent oral (PO SCOP). The purpose of this study was to determine and compare the efficacy, side effect profile, and pharmacotherapeutics of IN SCOP and PO SCOP. It was hypothesized that IN SCOP would rapidly achieve therapeutic concentrations at lower doses compared to PO SCOP while minimizing medication-induced performance impairment. Fifty-four aviation candidates were randomized to one of three treatment groups (0.4 mg IN SCOP gel, 0.8 mg PO SCOP or placebo) and then exposed to passive Coriolis cross-coupling. Medication efficacy, pharmacotherapeutics and side-effect profiles were tracked for all groups. Analysis revealed there were no significant differences in efficacy among groups. Pharmacotherapeutic data show increased scopolamine absorption and decreased time to reach maximum salivary concentration with intranasal administration, with no significant treatment side effects detected over time. There was a significant decrease in heart rate over time for IN SCOP and PO SCOP versus placebo, while no clinically significant differences were found for either systolic or diastolic blood pressures. In summary, IN SCOP absorption was significantly greater than PO SCOP with no detrimental impact on performance or side effects.

15. SUBJECT TERMS

motion sickness, motion sickness countermeasures, scopolamine, effects of scopolamine on cognition

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